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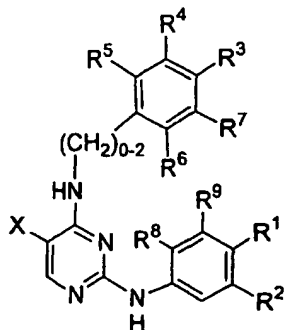
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(54) Title: 2-4-(DI-PHENYL-AMINO)-PYRIMIDINE DERIVATIVES USEFUL FOR TREATING HYPER-PROLIFERATIVE DISORDERS

(57) Abstract: The present invention relates to a 2-4-(diphenyl-amino)-pyrimidinyl compound of Formula I useful for treating hyper-proliferative disorders.



(i)

2-4-(Di-Phenyl-Amino)-Pyrimidine Derivatives Useful For Treating Hyper-Proliferative Disorders

This application claims priority from US provisional application 06/378329, filed May 6, 2002.

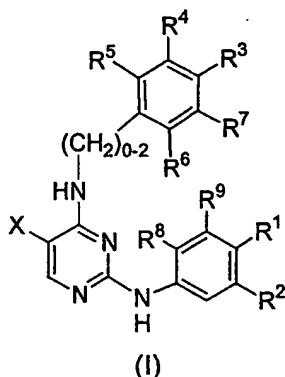
Field of the Invention

This invention relates to novel 2-4-(diphenyl-amino)-pyrimidinyl compounds, pharmaceutical compositions containing such compounds, and the use of those compounds and/or compositions for treating hyper-proliferative disorders.

Description of the Invention

Compounds of the Invention

One embodiment of this invention is a compound of Formula I



wherein

X is selected from (C<sub>1</sub>-C<sub>3</sub>)alkyl, CF<sub>3</sub>, and halo;

R<sup>1</sup> is H, OH, halo, CF<sub>3</sub>, C(O)R<sup>10</sup>, NR<sup>11</sup>R<sup>11</sup>, C(NH)NH<sub>2</sub>, C(N)OH, C(N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy,

S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, S(O)<sub>2</sub>NH<sub>2</sub>, indolyl, pyridyl, quinolyl,

(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with C(O)OH, (N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy, or with a five membered N containing heterocycle,

(C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with morpholinyl or with 1 or 2 substituents selected from OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy, 2 of said alkoxy

groups optionally being joined to form dimethyldioxolanyl,

a five membered heterocycle optionally substituted with 1 or

2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl group(s), said alkyl being

optionally substituted with an OH group;

a six membered heterocycle optionally substituted with C(O)OH,

C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl,

S(O)<sub>2</sub>-phenyl said phenyl being optionally substituted with 1 or 2  
 independently selected halo atoms, or  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups,  
 phenyl substituted with one substituent selected from (C<sub>1</sub>-C<sub>6</sub>)alkoxy, CF<sub>3</sub>, CN,  
 5 N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub> group, and  
 (C<sub>1</sub>-C<sub>3</sub>)alkyl optionally substituted with CN, and  
 O-pyridyl optionally substituted with halo or (C<sub>1</sub>-C<sub>3</sub>)alkoxy;  
 R<sup>2</sup> is H, S(O)<sub>2</sub>NH<sub>2</sub>, halo, ethynyl, OH, CF<sub>3</sub>, C(O)R<sup>10</sup>,  
 a five membered heterocycle, benzodioxolyl,  
 10 (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with C(O)OH, morpholinyl, with a five  
 membered N containing heterocycle, with  
 NH(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups, or with  
 (C<sub>1</sub>-C<sub>3</sub>)alkoxy, said alkoxy being optionally substituted with  
 morpholinyl or imidazole,  
 15 (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 substituents selected from  
 N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>, OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups  
 may optionally be joined to form dimethyldioxolanyl, or with  
 1 substituent selected from imidazolyl, pyrrolidinyl, morpholinyl and  
 piperidinyl,  
 20 NH(C<sub>1</sub>-C<sub>6</sub>)alkyl-six membered heterocycle optionally substituted  
 with C(O)OH, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
 S(O)<sub>2</sub>-phenyl said phenyl being optionally substituted at any  
 available C atom with 1 or 2 independently selected halo  
 atoms, or with  
 25 (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups,  
 phenyl substituted with 1 or 2 substituents independently selected from  
 (C<sub>1</sub>-C<sub>6</sub>)alkoxy, CN and halo, and  
 pyrazole optionally substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl;  
 R<sup>1</sup> and R<sup>2</sup> together with the C atoms to which each is attached may form a ring that is  
 30 fused to the phenyl ring to which they are attached to form a fused ring optionally  
 substituted with 1 or 2 substituents each independently selected from  
 (C<sub>1</sub>-C<sub>3</sub>)alkyl, (N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy, (C<sub>1</sub>-C<sub>3</sub>)alkyl-N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, C(O)NH<sub>2</sub>,  
 (N)OH, OH and SH,  
 and when the fused ring is indolyl, it may also be substituted with  
 35 (C<sub>1</sub>-C<sub>6</sub>)alkyl said alkyl being optionally substituted with 1 or 2 groups each  
 selected independently from OH, N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and

(C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups may optionally be joined to form dimethyldioxolanyl;

R<sup>3</sup> is selected from H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, halo, S(O)<sub>2</sub>NH<sub>2</sub>, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, CF<sub>3</sub>, morpholiny, piperaziny,

5 pyrazolyl optionally substituted with 1 or 2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl groups,

O-phenyl said phenyl being optionally substituted with halo, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, or C(O)O(C<sub>1</sub>-C<sub>3</sub>)alkyl,

(C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 substituents each independently

10 selected from OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups may optionally be joined to form dimethyldioxolanyl;

R<sup>4</sup> is selected from H, halo, ethynyl, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, or with pyrazolyl optionally substituted with 1 or 2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl groups, or

15 (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 OH group(s);

R<sup>3</sup> and R<sup>4</sup>, together with the C atoms to which each is attached, may form a ring that is fused to the phenyl ring to which they are attached to form a fused bi-cyclic heterocycle selected from

indolyl optionally substituted with

20 (C<sub>1</sub>-C<sub>6</sub>)alkyl said alkyl being optionally substituted with 1 or 2 groups each selected independently from OH, N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and (C<sub>1</sub>-C<sub>3</sub>)alkoxy, and wherein 2 of said alkoxy groups may optionally be joined to form dimethyldioxolanyl, and

25 benzotriazole optionally substituted with 1 or 2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl group(s);

and with the proviso that when R<sup>3</sup> and R<sup>4</sup> together form a cyclic moiety fused to the phenyl ring to which they are attached, then R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> must be H;

R<sup>5</sup> and R<sup>6</sup> are each independently selected from H, halo, and CF<sub>3</sub>;

30 R<sup>7</sup> is H, halo or (C<sub>1</sub>-C<sub>6</sub>)alkoxy;

R<sup>8</sup> is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, or halo;

R<sup>9</sup> is H, or (C<sub>1</sub>-C<sub>3</sub>)alkoxy;

R<sup>10</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, OH, NH<sub>2</sub>, NHOR<sup>12</sup>, NHNHC(O)(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with CN, or

35 NH(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH group(s);

R<sup>11</sup> is selected from H, C(O)R<sup>10</sup>, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>3</sub>)alkyl, S(O)<sub>2</sub>N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>,

S(O)<sub>2</sub>-five membered heterocycle said heterocycle being optionally substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl and NHC(O) (C<sub>1</sub>-C<sub>3</sub>)alkyl,

R<sup>12</sup> is selected from H, (C<sub>1</sub>-C<sub>3</sub>)alkyl, and tetrahydropyranyl;

Y is N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>, imidazolyl, piperidinyl, morpholinyl, pyrrolidinyl,

5 NH-phenyl-(C<sub>1</sub>-C<sub>6</sub>)alkoxy, NH-O-phenyl-(C<sub>1</sub>-C<sub>6</sub>)alkoxy? or  
NH-(C<sub>1</sub>-C<sub>6</sub>)alkoxy-phenyl;

with the provisos that

- a) when R<sup>1</sup> is H then R<sup>2</sup> must be other than H;
- b) when R<sup>2</sup> is H then R<sup>1</sup> must be other than H;
- 10 c) when R<sup>3</sup> is H then R<sup>4</sup> must be other than H;
- d) when R<sup>4</sup> is H then R<sup>3</sup> must be other than H;
- e) when R<sup>1</sup> is C(O)OH then at least one of R<sup>2</sup>, R<sup>8</sup> and R<sup>9</sup> must be other than H;
- f) when R<sup>2</sup> is C(O)OH then at least one of R<sup>1</sup>, R<sup>8</sup> and R<sup>9</sup> must be other than H;
- g) when R<sup>2</sup> is OCH<sub>2</sub>CH<sub>2</sub>Y, then R<sup>1</sup> must be other than H;
- 15 h) when R<sup>1</sup> and R<sup>2</sup> are fused then R<sup>8</sup> and R<sup>9</sup> are each H; and
- i) when R<sup>1</sup> is S(O)<sub>2</sub>NH<sub>2</sub>, and when (CH<sub>2</sub>)<sub>0-2</sub> is zero, then at least one of R<sup>3</sup> and R<sup>4</sup> must be selected from morpholinyl, pyrazolyl, and optionally substituted O-phenyl, or R<sup>3</sup> and R<sup>4</sup> together with the C atoms to which each is attached, must form a ring that is fused to the phenyl group to which they are attached
- 20 to form optionally substituted indolyl or benzotriazole;

or a pharmaceutically acceptable salt thereof.

A preferred embodiment of this invention is a compound of Formula I wherein

- X is halo,
- 25 R<sup>1</sup> is selected from H, OH, C(O)R<sup>10</sup>, NR<sup>11</sup>R<sup>11</sup>, C(N)OH, C(N)(C<sub>1</sub>-C<sub>6</sub>)alkoxy, indolyl, pyridyl, quinolyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with C(O)OH, (N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy, or with a five membered N containing heterocycle, (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with morpholinyl or with 1 or 2 substituents
- 30 selected from OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy, 2 of said alkoxy groups optionally being joined to form dimethyldioxolanyl, a five membered heterocycle optionally substituted with 1 or 2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl group(s), said alkyl being optionally substituted with an OH group;
- 35 a six membered heterocycle optionally substituted with C(O)OH, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups,

phenyl substituted with one substituent selected from (C<sub>1</sub>-C<sub>6</sub>)alkoxy, CN,  
and N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>;

R<sup>2</sup> is selected from H, OH, CF<sub>3</sub>, C(O)R<sup>10</sup>, a five membered heterocycle,

(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with C(O)OH, morpholinyl, with a five

5 membered N containing heterocycle, with

NH(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups, or with

(C<sub>1</sub>-C<sub>3</sub>)alkoxy, said alkoxy being optionally substituted with

morpholinyl or imidazole,

(C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 substituents selected from

10 N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>, OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups

may optionally be joined to form dimethyldioxolanyl, or with

1 substituent selected from imidazolyl, pyrrolidinyl, morpholinyl and

piperadinyl,

NH(C<sub>1</sub>-C<sub>6</sub>)alkyl-six membered heterocycle,

15 phenyl substituted with 1 or 2 substituents independently selected from

(C<sub>1</sub>-C<sub>6</sub>)alkoxy, CN and halo, and

pyrazole optionally substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl;

R<sup>1</sup> and R<sup>2</sup> together with the C atoms to which each is attached may form a ring that

is fused to the phenyl ring to which they are attached to form a fused ring

20 optionally substituted with 1 or 2 substituents each independently selected from

(C<sub>1</sub>-C<sub>3</sub>)alkyl, (N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy, (C<sub>1</sub>-C<sub>3</sub>)alkyl-N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, C(O)NH<sub>2</sub>,

(N)OH, and (N)O(C<sub>1</sub>-C<sub>3</sub>)alkyl,

and when the fused ring is indolyl, it may also be substituted with

(C<sub>1</sub>-C<sub>6</sub>)alkyl said alkyl being optionally substituted with 1 or 2 groups each

25 selected independently from OH, N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and

(C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups may

optionally be joined to form dimethyldioxolanyl;

R<sup>3</sup> is selected from H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, halo, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, morpholinyl, piperazinyl,

pyrazolyl optionally substituted with 1 or 2 independently selected

30 (C<sub>1</sub>-C<sub>6</sub>)alkyl groups,

O-phenyl said phenyl being optionally substituted with halo, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, or

C(O)O(C<sub>1</sub>-C<sub>3</sub>)alkyl,

(C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 substituents each independently

selected from OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups may

35 optionally be joined to form dimethyldioxolanyl;

R<sup>4</sup> is selected from H, halo, ethynyl, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl,

(C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 OH group(s), and  
pyrazolyl optionally substituted with 1 or 2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl  
groups;

R<sup>3</sup> and R<sup>4</sup>, together with the C atoms to which each is attached, may form a ring that  
is fused to the phenyl ring to which they are attached to form a fused bi-cyclic  
heterocycle selected from

indolyl optionally substituted with

(C<sub>1</sub>-C<sub>6</sub>)alkyl said alkyl being optionally substituted with 1 or 2  
groups each selected independently from OH,

N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and (C<sub>1</sub>-C<sub>3</sub>)alkoxy, and

wherein 2 of said alkoxy groups may optionally be joined to  
form dimethyldioxolanyl, and

benzotriazole;

R<sup>5</sup> and R<sup>6</sup> are each H;

R<sup>7</sup> is selected from H, halo and (C<sub>1</sub>-C<sub>6</sub>)alkoxy;

R<sup>8</sup> is H;

R<sup>9</sup> is selected from H and (C<sub>1</sub>-C<sub>3</sub>)alkoxy;

R<sup>10</sup> is selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, NHOR<sup>12</sup>, (C<sub>1</sub>-C<sub>6</sub>)alkoxy and

NH(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH group(s);

R<sup>11</sup> is selected from H, C(O)R<sup>10</sup>, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>3</sub>)alkyl, S(O)<sub>2</sub>N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and

S(O)<sub>2</sub>-five membered heterocycle said heterocycle being optionally

substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl and NHC(O) (C<sub>1</sub>-C<sub>3</sub>)alkyl;

R<sup>12</sup> is selected from H, (C<sub>1</sub>-C<sub>3</sub>)alkyl, and tetrahydropyranyl; and

Y is selected from N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>, imidazolyl, piperidinyl, and morpholinyl.

The terms identified above have the following meaning throughout:

The term "optionally substituted" means that the moiety so modified may have  
from none to up to about the highest number of substituents indicated. When there are  
two or more substituents on any moiety, each substituent is chosen independently of any  
other substituent and can, accordingly, be the same or different.

The terms "(C<sub>1</sub>-C<sub>3</sub>)alkyl" and "(C<sub>1</sub>-C<sub>6</sub>)alkyl", mean linear or branched saturated  
carbon groups having from about 1 to about 3 or about 6 C atoms, respectively. Such  
groups include but are not limited to methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl,  
*sec*-butyl, *tert*-butyl, and the like.

The terms "(C<sub>1</sub>-C<sub>3</sub>)alkoxy" and "(C<sub>1</sub>-C<sub>6</sub>)alkoxy" mean a linear or branched  
saturated carbon group having from about 1 to about 3 or about 6 C atoms, said carbon

group being attached to an O atom. The O atom is the point of attachment of the alkoxy substituent to the pyridyl ring. Such groups include but are not limited to methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy, and the like.

5 The terms "(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted" and "(C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted" mean an alkyl group or an alkoxy group, respectively, as defined above, wherein each C atom is bonded to 1, 2 or 3 H atoms, as appropriate, or any H atom up to about the recited maximum number of H atoms on a C atom may be replaced with a recited substituent, or the alkyl or alkoxy groups may be substituted as otherwise described herein, with the proviso that combinations of recited substituents result in a  
10 chemically stable compound.

The term "halo" means an atom selected from Cl, Br, F and I, where Cl, Br and F are preferred.

When "(N)" "(NH)" and "(O)" are used in a chemical formula, they mean =N, =NH and =O respectively.

15 The formula "N[C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>" and N[S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>", and the like, mean that each of the 2 possible alkyl groups attached to the N atom are selected independently from the other so that they may be the same or they may be different.

The term "five membered heterocycle" means an aromatic, saturated or partially saturated ring containing about 5 atoms and having 1, 2 or 3 heteroatom(s) each selected  
20 independently from O, N, and S, the rest being C atoms, with the proviso that there can be no more than 1 O atom or 1 S atom in the heterocycle. This heterocycle is attached through any available C or N atom to the rest of the molecule and is optionally substituted at any available C or N atom with the recited substituents. Such groups include pyrrolyl, furanyl, thiophenyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl, dihydroisoxazolyl,  
25 isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, and the like, in all their possible isomeric forms.

The term "six membered heterocycle" means a saturated or partially unsaturated ring containing about 6 atoms, 1 or 2 of which are each independently selected from N, O, and S, the rest being C atoms. There can be no more than 2 O atoms or 2 S atoms in  
30 any heterocycle, and when there are 2 O atoms in a heterocycle, they must be non-adjacent. This ring is attached through any available C or N atom to the rest of the molecule and is optionally substituted with the recited substituents on any available C and/or N atom. This heterocycle includes piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl and the like.

The term "five membered N containing heterocycle" means a saturated or partially saturated ring containing about 5 atoms, 1, 2, or 3 of which are N atoms, the rest being C, where the heterocycle is attached through any available C or N atom to the rest of the molecule. Such groups include imidazolyl, pyrrolidinyl, and the like.

5           The term "fused ring" means a group having from 9 to 14 atoms divided into 2 or 3 chemically stable rings, one of which is the phenyl ring to which R<sup>1</sup> and R<sup>2</sup> are attached. Each ring is fused to another ring through adjacent C, C-N or N atoms and 3, 2 or 1 of the remaining atoms, respectively, in the fused ring are heteroatoms each independently selected from N or O, with the proviso that there can be no more than 1 O atom in any  
10 fused heterocycle. The heteroatoms may be located at any available position in the fused moiety other than in the phenyl ring to which R<sup>1</sup> and R<sup>2</sup> are attached. When the fused ring is bicyclic, the one ring that is fused to the phenyl ring to which R<sup>1</sup> and R<sup>2</sup> are attached may be either aromatic, partially saturated or saturated. That is, if the one ring stood alone, it could be either aromatic partially saturated, or saturated. When the fused  
15 ring is tri-cyclic, the bicyclic ring that is fused to the phenyl ring to which R<sup>1</sup> and R<sup>2</sup> are attached may be either unsaturated or partially saturated. That is, if the bicyclic ring stood alone, it could be either partially saturated or saturated. The resulting fused bi- or tri-cyclic ring is optionally substituted with the recited substituents at any available C and/or N atom(s). Such groups include but are not limited to benzimidazolyl, benzimidazolyl-2-one, indolin-2-one, benzotriazolyl, dihydrobenzoindazolyl, dihydrobenzodioxinyl, dihydroinden-1-oneoxime, dihydronaphthalenone, dihydrobenzoindazolyl, tetrahydropyrrolbenzoxazinyl,  
20 indazolyl, benzotriazolyl, benzocyclopentyl, benzocyclohexyl, indolyl and the like.

25           When a phenyl ring may be substituted with one or more substituent, the substituent(s) may be attached to the phenyl ring at any available C atom, preferably at the 3, 4, or 5 C. When there is more than 1 substituent on a phenyl ring, each is selected independently from the other so that they may be the same or different.

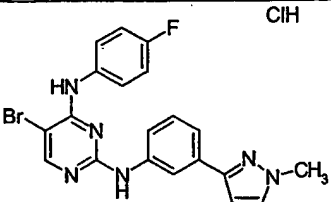
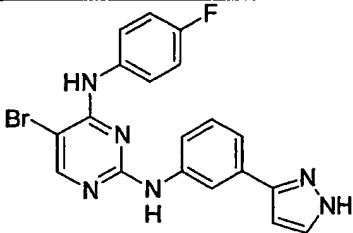
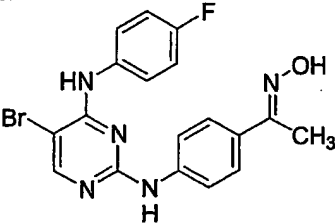
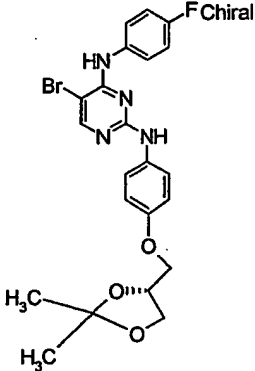
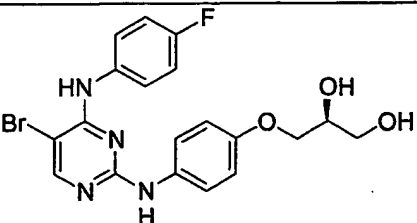
The term "five membered N containing heterocycle" means a saturated or partially saturated ring containing about 5 atoms, 1, 2, or 3 of which are N atoms, the rest being C, where the heterocycle is attached through any available C or N atom to the rest of the molecule. Such groups include imidazolyl, pyrrolidinyl, and the like.

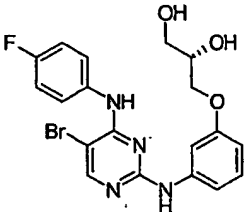
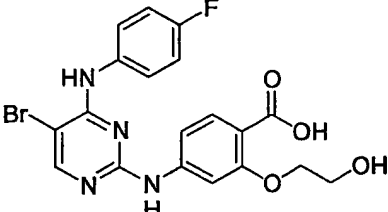
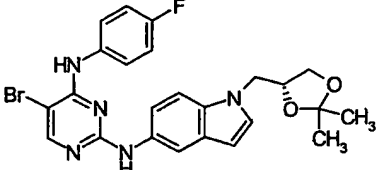
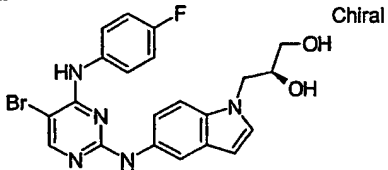
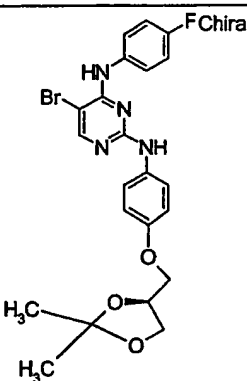
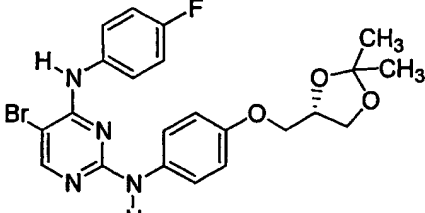
5       The term "fused ring" means a group having from 9 to 14 atoms divided into 2 or 3 chemically stable rings, one of which is the phenyl ring to which R<sup>1</sup> and R<sup>2</sup> are attached. Each ring is fused to another ring through adjacent C, C-N or N atoms and 3, 2 or 1 of the remaining atoms, respectively, in the fused ring are heteroatoms each independently selected from N or O, with the proviso that there can be no more than 1 O atom in any  
10       fused heterocycle. The heteroatoms may be located at any available position in the fused moiety other than in the phenyl ring to which R<sup>1</sup> and R<sup>2</sup> are attached. When the fused ring is bicyclic, the one ring that is fused to the phenyl ring to which R<sup>1</sup> and R<sup>2</sup> are attached may be either aromatic, partially saturated or saturated. That is, if the one ring stood alone, it could be either aromatic partially saturated, or saturated. When the fused  
15       ring is tri-cyclic, the bicyclic ring that is fused to the phenyl ring to which R<sup>1</sup> and R<sup>2</sup> are attached may be either unsaturated or partially saturated. That is, if the bicyclic ring stood alone, it could be either partially saturated or saturated. The resulting fused bi- or tri-cyclic ring is optionally substituted with the recited substituents at any available C and/or N atom(s). Such groups include but are not limited to benzimidazolyl, benzimidazolyl-2-one, indolin-2-one, benzotriazolyl, dihydrobenzoindazolyl, dihydrobenzodioxinyl, dihydroinden-1-oneoxime, dihydronaphthalenone, dihydrobenzoindazolyl, tetrahydropyrrolobenzoxazinyl, indazolyl, benzotriazolyl, benzocyclopentyl, benzocyclohexyl, indolyl and the like.

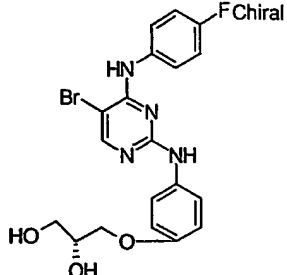
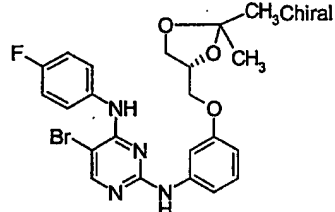
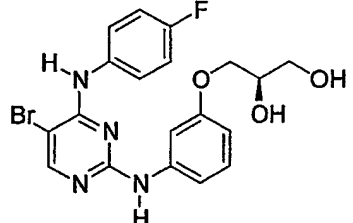
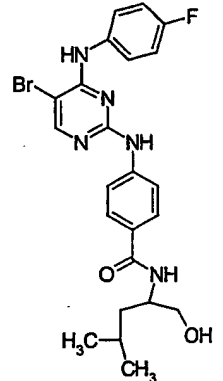
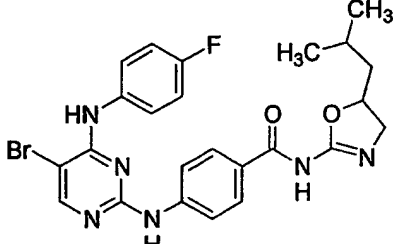
25       When a phenyl ring may be substituted with one or more substituent, the substituent(s) may be attached to the phenyl ring at any available C atom, preferably at the 3, 4, or 5 C. When there is more than 1 substituent on a phenyl ring, each is selected independently from the other so that they may be the same or different.

Representative compounds of Formula I are shown in Table I

Table 1

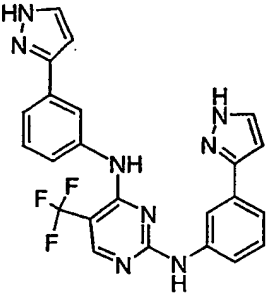
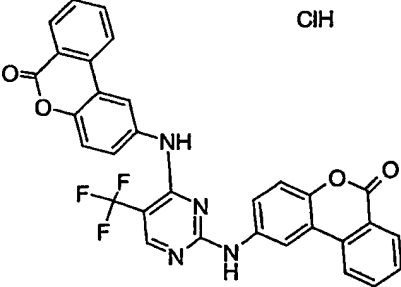
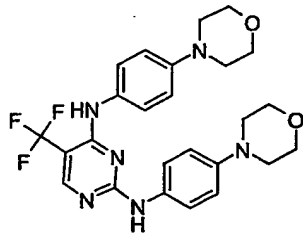
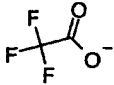
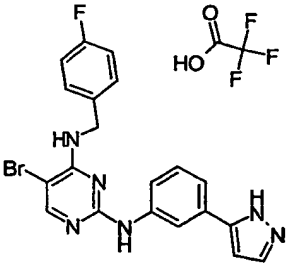
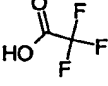
Example No.	Structures	Characterization <sup>a</sup>	Method
1	 <p>ClH</p>	<p>(M+H)<sup>+</sup> 439.2  RT 2.56 min  TLC R<sub>f</sub> 0.40 (50% EtOAc/HEX)</p>	B3, 1b, 1c
2		R <sub>f</sub> 0.70 (EtOAc)	2
3		R <sub>f</sub> 0.54 (EtOAc/HEX 1/1)	3
4	 <p>F Chiral</p>	<p>(M+H)<sup>+</sup> 489.6  RT 2.57 min  TLC R<sub>f</sub> 0.59 (50% EtOAc/HEX)</p>	1b, 1c, 4
5		—	5

Example No.	Structures	Characterization <sup>a</sup>	Method
6	 <p>Chiral</p>	$(M+H)^+$ 449.5 RT 2.08 min TLC R <sub>f</sub> 0.72 (10% MeOH/90% CHCl <sub>3</sub> ) mp = 157-158 °C	1b, 1c
8		—	8
9	 <p>Chiral</p>	$(M+H)^+$ 512.3 RT 2.58 min TLC R <sub>f</sub> 0.29 (50% EtOAc/HEX) mp = 130-132 °C	9
10	 <p>Chiral</p>	$(M+H)^+$ 472.4 RT 2.08 min TLC R <sub>f</sub> 0.29 (50% EtOAc/HEX)	4, B1, 1b, 1c
11	 <p>Chiral</p>	$(M+H)^+$ 489.6 RT 2.89 min TLC R <sub>f</sub> 0.51 (50% EtOAc/HEX)	1b, 1c, 4
13		mp 95-116.5 °C RT 2.6 min	13

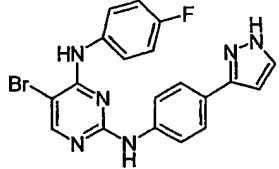
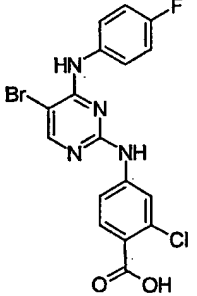
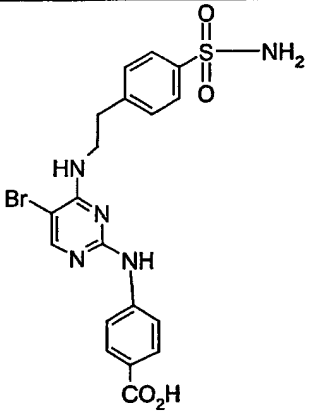
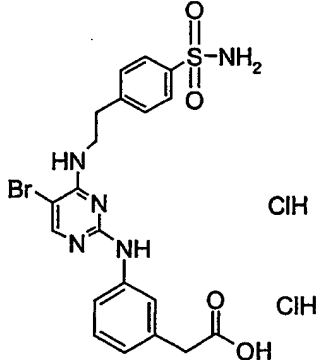
Example No.	Structures	Characterization <sup>a</sup>	Method
14		$(M+H)^+$ 449.5 RT 1.90 min TLC R <sub>f</sub> 0.47 (20% MeOH/80% CHCl <sub>3</sub> ) mp = 201 °C	1b, 1c
15		$(M+H)^+$ 489.5 RT 2.87 min TLC R <sub>f</sub> 0.52 (50% EtOAc/HEX)	1b, 1c, 4
16		RT 2.1 min	16
17		$(M+H)^+$ 458.8 RT 2.62 min TLC R <sub>f</sub> 0.22 (50% EtOAc/Hex)	1b, 1c, 17a, 17b
18		—	18

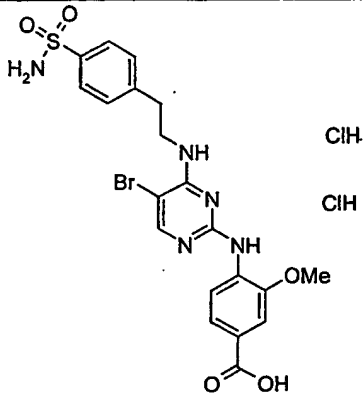
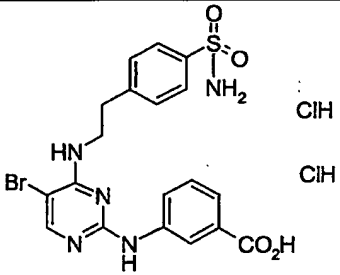
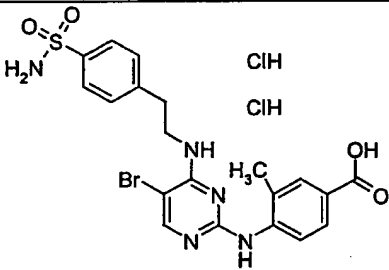
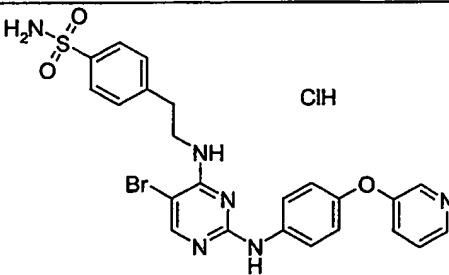
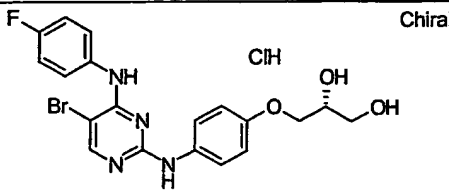
Example No.	Structures	Characterization <sup>a</sup>	Method
19		$(M+H)^+$ 484.2 RT 2.61 min TLC R <sub>f</sub> 0.56 (50% Hex/EtOAc)	1b, 1c, 17a, 17b, 18
20		$(M+H)^+$ 667 R <sub>f</sub> = 0.34 (45/50/5 MeOH/CH <sub>3</sub> CN/H <sub>2</sub> O) <sup>b</sup>	B7a, B7b, N4, B7c, 19, 20
21		$(M+H)^+$ 477 R <sub>f</sub> = 0.34 (4/1 Hex/EtOAc)	21
22		RT 2.56 min $(M+H)^+$ 386	22
23		RT 0.32 min $(M+H)^+$ 344	22, 23

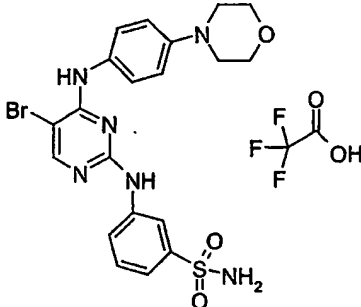
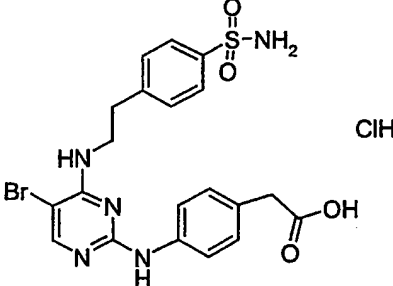
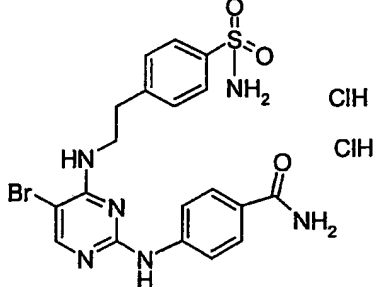
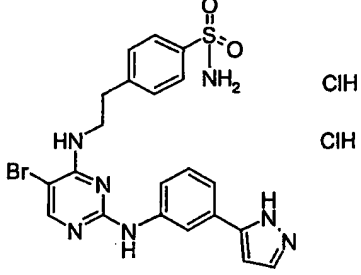
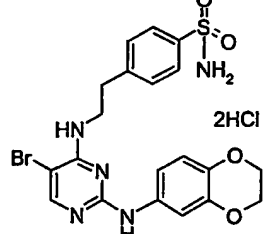
Example No.	Structures	Characterization <sup>a</sup>	Method
24		RT 2.11 min [M+H] <sup>+</sup> 450.3	24
25		RT 2.56 (M+H) <sup>+</sup> 598.0	22, 23, 25
26		RT 2.90 (M+H) <sup>+</sup> 646.0	22, 23, 26
27		RT 2.78 (M+H) <sup>+</sup> 557.3	22, 27
28		RT 1.91 (M+H) <sup>+</sup> 453.2	28, 22

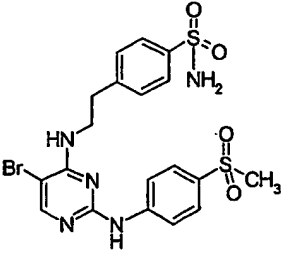
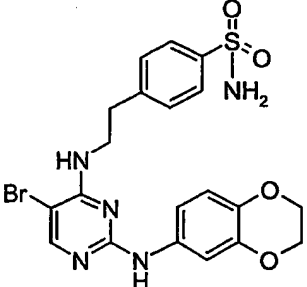
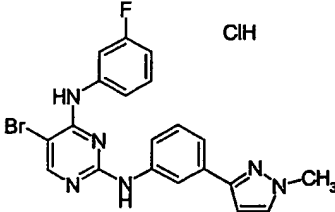
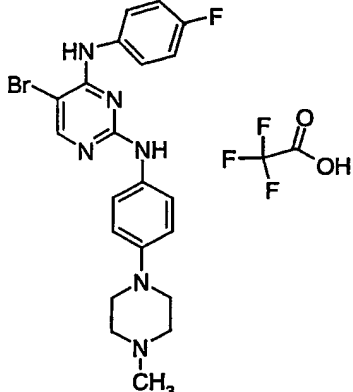
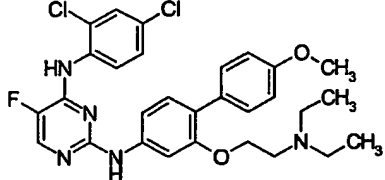
Example No.	Structures	Characterization <sup>a</sup>	Method
29		$(M+H)^+$ 463.0 $R_f$ 0.61 (1/9/90 TFA/MeOH/CH <sub>2</sub> Cl <sub>2</sub> )	1a
30	 ClH	$(M+H)^+$ 567 $R_f$ 0.70 (1/9/90 TFA/MeOH/CH <sub>2</sub> Cl <sub>2</sub> ) RT 2.96	1a
31	 	$(M+H)^+$ 501.4 $R_f$ 0.28 (1/1 EtOAc/Hex)	1a
32	 	$(M+H)^+$ 439.1 RT 2.36 min TLC $R_f$ 0.70 (EtOAc)	1b, 1c

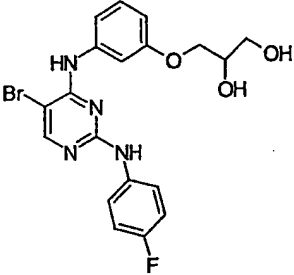
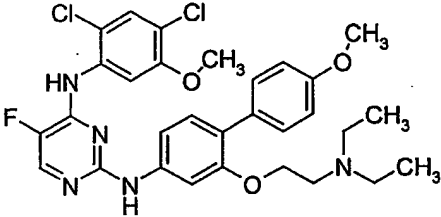
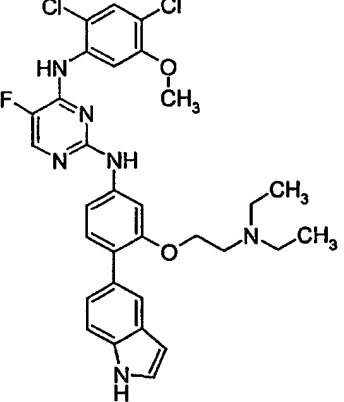
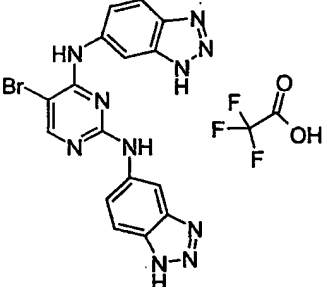
Example No.	Structures	Characterization <sup>a</sup>	Method
33		$(M+H)^+$ 471.2 RT 1.87 min TLC R <sub>f</sub> 0.22 (10% MeOH/EtOAc)	1b, 1c
34		$(M+H)^+$ 340.2 RT 1.85 min TLC R <sub>f</sub> 0.29 (50% EtOAc/Hex)	1b, 1c
35		$(M+H)^+$ 340.2 RT 1.85 min TLC R <sub>f</sub> 0.29 (50% EtOAc/Hex)	1b, 1c
36		$(M+H)^+$ 414.4 RT 2.41 min TLC R <sub>f</sub> 0.29 (50% Hex/EtOAc)	1b, 1c
37		$(M+H)^+$ 428.1 RT 2.20 min TLC R <sub>f</sub> 0.55 (50% Hex/EtOAc)	1b, 1c

Example No.	Structures	Characterization <sup>a</sup>	Method
38		$(M+H)^+$ 425.2 RT 2.47 min TLC R <sub>f</sub> 0.76 (EtOAc) mp = >240 °C	B3, 1b, 1c
39	 ClH	$(M+H)^+$ 449.2 RT 2.54 min TLC R <sub>f</sub> 0.84 (20% MeOH/ 80% CH <sub>2</sub> Cl <sub>2</sub> ) mp > 220 °C	1b, 1c
40		$(M+H)^+$ 492.2 RT 1.94 min TLC R <sub>f</sub> 0.03 (50% EtOAc/Hex)	1b, 1c
41	 ClH ClH	$(M+H)^+$ 506.1 RT 1.86 min TLC R <sub>f</sub> 0.11 (67% EtOAc/Hex)	1b, 1c

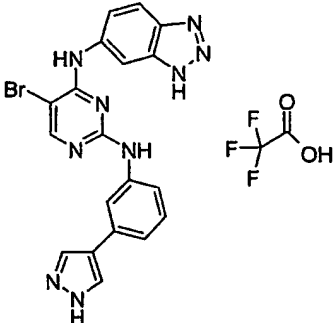
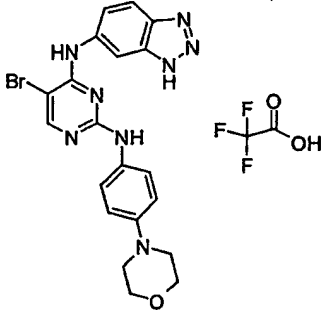
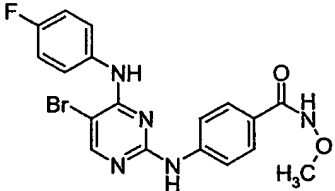
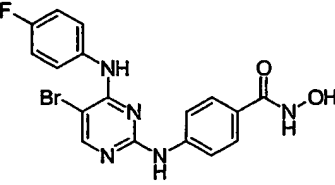
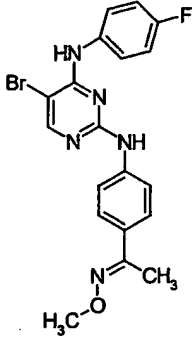
Example No.	Structures	Characterization <sup>a</sup>	Method
42	 <chem>COc1ccc(cc1)Nc2nc(NCc3ccc(S(=O)(=O)N)cc3)cnc2Br</chem> 2 ClH	$(M+H)^+$ 522.0 RT 2.05 min TLC R <sub>f</sub> 0.11 (67% EtOAc/Hex)	1b, 1c
43	 <chem>OC(=O)c1ccc(cc1)Nc2nc(NCc3ccc(S(=O)(=O)N)cc3)cnc2Br</chem> 2 ClH	$(M+H)^+$ 526.9 RT 1.77 min TLC R <sub>f</sub> 0.32 (67% EtOAc/Hex)	1b, 1c
44	 <chem>CC1=CC=C(C(=O)O)C=C1Nc2nc(NCc3ccc(S(=O)(=O)N)cc3)cnc2Br</chem> 2 ClH	$(M+H)^+$ 506.0 RT 1.90 min TLC R <sub>f</sub> 0.17 (67% EtOAc/Hex)	1b, 1c
45	 <chem>c1ccc(cc1)Oc2ccc(cc2)Nc3nc(NCc4ccc(S(=O)(=O)N)cc4)cnc3Br</chem> 2 ClH	$(M+H)^+$ 541.2 RT 1.81 min TLC R <sub>f</sub> 0.27 (67% EtOAc/Hex)	1b, 1c
46	 <chem>OC[C@H](O)COc1ccc(cc1)Nc2nc(NCc3ccc(S(=O)(=O)N)cc3)cnc2Br</chem> 2 ClH, Chiral	$(M+H)^+$ 449.2 RT 2.54 min TLC R <sub>f</sub> 0.13 (50% Hex/EtOAc) mp > 220 °C	1b, 1c, 6

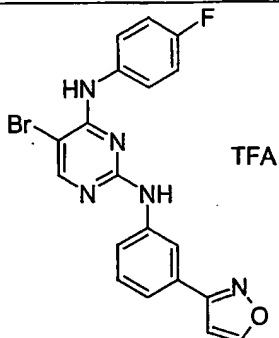
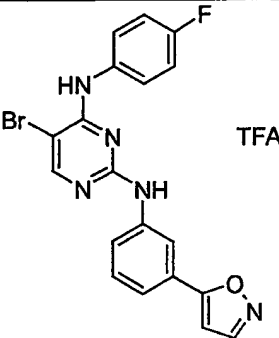
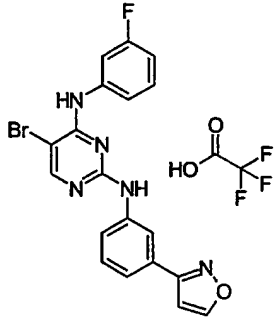
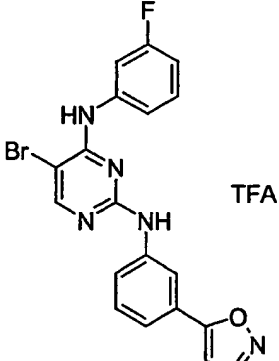
Example No.	Structures	Characterization <sup>a</sup>	Method
47		(M+H) <sup>+</sup> 507.0 RT 2.19 min	1b, 1c
48		(M+H) <sup>+</sup> 506.1 RT 1.94 min TLC R <sub>f</sub> : streaks (67% EtOAc/Hex)	1b, 1c
49		(M+H) <sup>+</sup> 493.0 RT 1.71 min TLC R <sub>f</sub> : streaks (67% EtOAc/Hex)	1b, 1c
50		(M+H) <sup>+</sup> 514.01 RT 2.04 min TLC R <sub>f</sub> : streaks (67% EtOAc/Hex)	1b, 1c
51		(M+H) <sup>+</sup> 492.2 RT 2.49 min TLC R <sub>f</sub> 0.09 (67% EtOAc/Hex)	1b, 1c

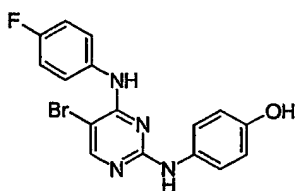
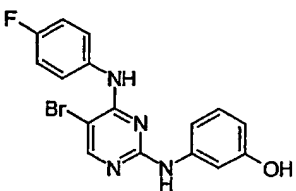
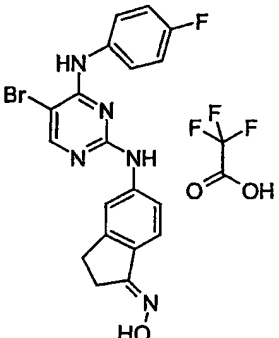
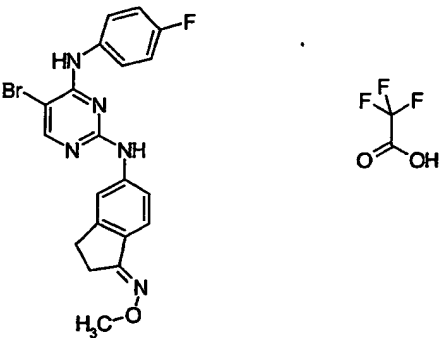
Example No.	Structures	Characterization <sup>a</sup>	Method
52		$(M+H)^+$ 526.2 RT 2.69 min TLC R <sub>f</sub> 0.40 (67% EtOAc/Hex)	1b, 1c
53	 ClH	$(M+H)^+$ 506.3 RT 2.66 min TLC R <sub>f</sub> 0.60 (67% EtOAc/Hex)	1b, 1c
54	 ClH	$(M+H)^+$ 439.2 RT 2.76 min TLC R <sub>f</sub> 0.40 (50% EtOAc/HEX)	B3, 1b, 1c
55		$(M+H)^+$ 457.2 RT 1.74 min	1b, 1c
56		$(M+H)^+$ 570 R <sub>f</sub> = 0.32 (50/49/1 MeOH/CH <sub>3</sub> CN/H <sub>2</sub> O)	B7a, B7b, N4, B7c, 19, 20

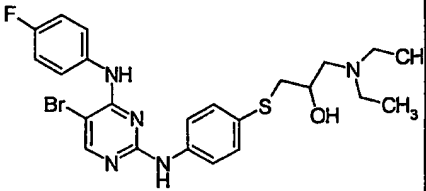
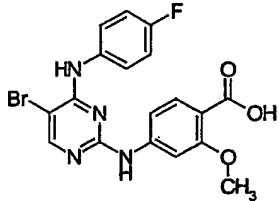
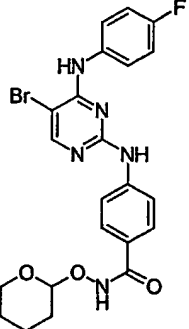
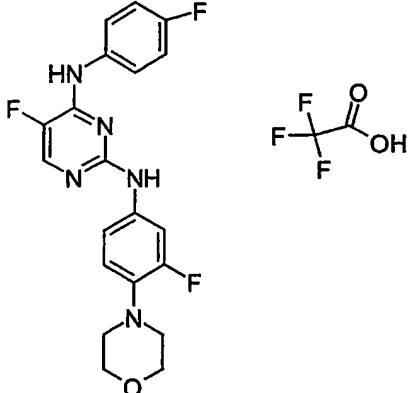
Example No.	Structures	Characterization <sup>a</sup>	Method
57		$(M+H)^+$ 449.3 RT 1.77 min TLC R <sub>f</sub> 0.45 (10% MeOH/90% CHCl <sub>3</sub> )	1b, 1c
58		$(M+H)^+$ 601 R <sub>f</sub> = 0.35 (50/45/5 MeOH/CH <sub>3</sub> CN/H <sub>2</sub> O)	B7a, B7b, N4, B7c, 19, 20
59		$(M+H)^+$ 609 RT 2.52 min. <sup>a</sup>	B7a, B7b, N4, B7c, 1a, 1c
60		$(M+H)^+$ 423.2 RT 2.20 min TLC R <sub>f</sub> 0.51 (10% MeOH/EtOAc)	1b, 1c

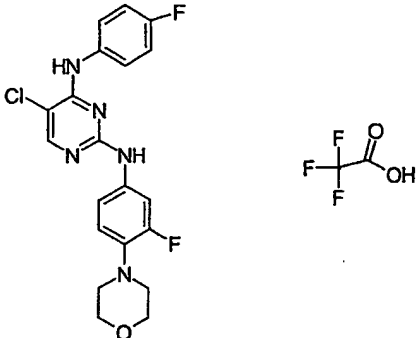
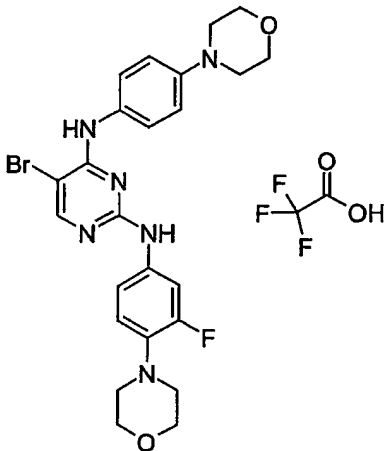
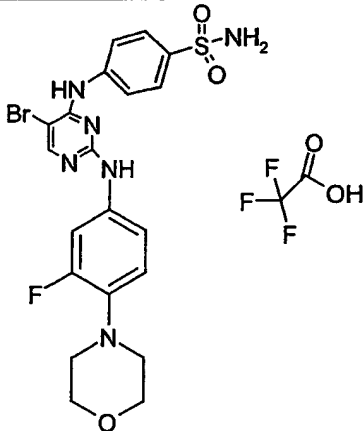
Example No.	Structures	Characterization <sup>a</sup>	Method
61		(M+H) <sup>+</sup> 381.4 RT 2.28 min	1b, 1c
62		((M+H) <sup>+</sup> 413.1 RT 3.18 min TLC R <sub>f</sub> 0.3048 (20 % EtOAc/Hex)	1b, 1c
63		((M+H) <sup>+</sup> 413.1 RT 2.69 min TLC R <sub>f</sub> 0.1359 (20 % EtOAc/Hex)	1b, 1c
64		(M+H) <sup>+</sup> 433.1 RT 2.63 min TLC R <sub>f</sub> 0.38 (EtOAc)	1b, 1c
65		(M+H) <sup>+</sup> 450.3 RT 2.78 min TLC R <sub>f</sub> 0.86 (20% MeOH/EtOAc)	1b, 1c

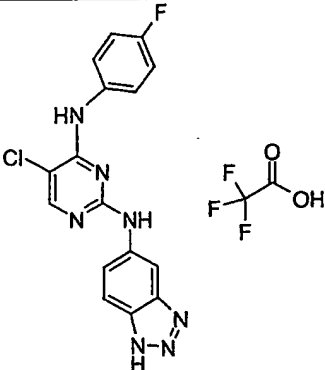
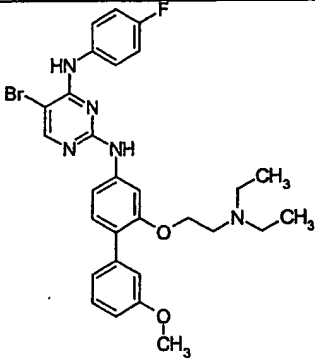
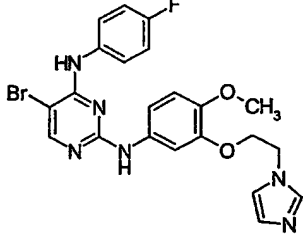
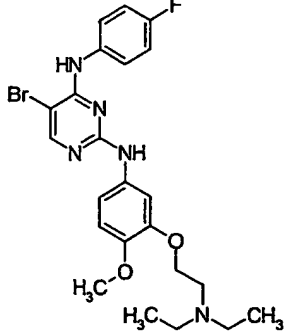
Example No.	Structures	Characterization <sup>a</sup>	Method
66		<p>(M+H)<sup>+</sup> 448.0  RT 2.04 min  TLC R<sub>f</sub> 0.70 (10% MeOH/EtOAc)</p>	1b, 1c
67		<p>(M+H)<sup>+</sup> 467.1  RT 1.88 min  TLC R<sub>f</sub> 0.80 (10% MeOH/EtOAc)</p>	1b, 1c
68		<p>(M+H)<sup>+</sup> 432.0  RT 2.67min  TLC R<sub>f</sub> 0.2678 (2% MeOH/CH<sub>2</sub>Cl<sub>2</sub>)</p>	1b, 1c
69		<p>(M+H)<sup>+</sup> 418.0  RT 2.92min  TLC R<sub>f</sub> 0.6250 (2% MeOH/CH<sub>2</sub>Cl<sub>2</sub>)</p>	1b, 1c
70		<p>(M+H)<sup>+</sup> 430.2  RT 2.98 min  TLC R<sub>f</sub> 0.59 (50% EtOAc/HEX)</p>	1b, 1c, 7

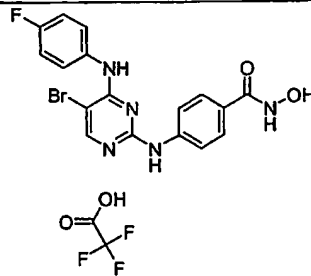
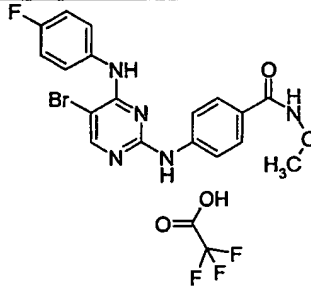
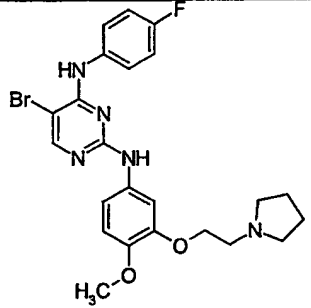
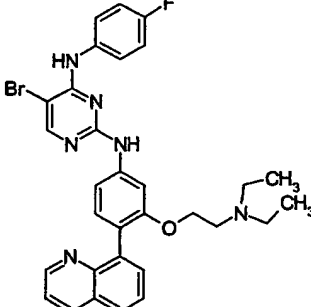
Example No.	Structures	Characterization <sup>a</sup>	Method
71	 <p>TFA</p>	(M+H) <sup>+</sup> 426.4 RT 2.68 min TLC R <sub>f</sub> 0.68 (50% EtOAc/HEX)	B3, 1b, 1c
72	 <p>TFA</p>	(M+H) <sup>+</sup> 426.2 RT 2.71 min TLC R <sub>f</sub> 0.68 (50% EtOAc/HEX)	B3, 1b, 1c
73	 <p>TFA</p>	(M+H) <sup>+</sup> 426.5 RT 2.91 min TLC R <sub>f</sub> 0.71 (50% EtOAc/HEX)	B3, 1b, 1c
74	 <p>TFA</p>	(M+H) <sup>+</sup> 426.3 RT 2.95 min TLC R <sub>f</sub> 0.71 (50% EtOAc/HEX)	B3, 1b, 1c

Example No.	Structures	Characterization <sup>a</sup>	Method
75	<p>ClH</p> 	<p>(M+H)<sup>+</sup> 375.2 RT 1.98 min TLC R<sub>f</sub> 0.78 (20% MeOH/80% CHCl<sub>3</sub>) mp = 245 °C</p>	1b, 1c
76	<p>ClH</p> 	<p>(M+H)<sup>+</sup> 375.4 RT 2.17 min TLC R<sub>f</sub> 0.78 (20% MeOH/80% CHCl<sub>3</sub>) mp = 246 °C</p>	1b, 1c
77		<p>(M+H)<sup>+</sup> 428.4 RT 2.41 min TLC R<sub>f</sub> 0.37 (50% EtOAc/HEX)</p>	1b, 1c, 7
78		<p>(M+H)<sup>+</sup> 442.1 RT 2.91 min TLC R<sub>f</sub> 0.40 (50% EtOAc/HEX)</p>	1b, 1c, 7

Example No.	Structures	Characterization <sup>a</sup>	Method
79	<p>ClH</p> 	<p>(M+H)<sup>+</sup> 520.0 RT 2.15 min TLC R<sub>f</sub> 0.31 (20% MeOH/80% CHCl<sub>3</sub>) mp = 86 °C</p>	1b, 1c
80		<p>(M+H)<sup>+</sup> 433.4 RT 2.52 min TLC R<sub>f</sub> 0.38 (EtOAc)</p>	1b, 1c
81		<p>(M+H)<sup>+</sup> 418.0 RT 2.67 min TLC R<sub>f</sub> 0.2678 (2% MeOH/CH<sub>2</sub>Cl<sub>2</sub>)</p>	1b, 1c
82		<p>(M+H)<sup>+</sup> 402.3 RT 2.25 min TLC R<sub>f</sub> 0.60 (10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>)</p>	1b, 1c

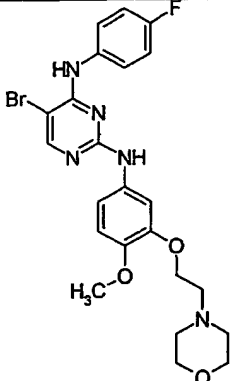
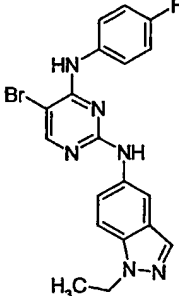
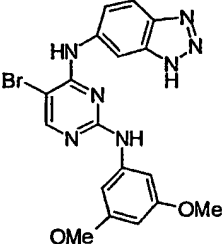
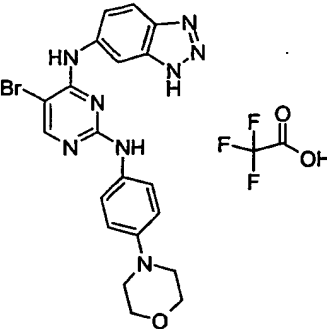
Example No.	Structures	Characterization <sup>a</sup>	Method
83		(M+H) <sup>+</sup> 418.5 RT 2.50 min TLC R <sub>f</sub> 0.71 (10% MeOH/CH <sub>2</sub> Cl <sub>2</sub> )	1b, 1c
84		(M+H) <sup>+</sup> 531.3 RT 2.22 min TLC R <sub>f</sub> 0.49 (50% Hex/EtOAc)	1b, 1c
85		(M+H) <sup>+</sup> 523.5 RT 2.21 min TLC R <sub>f</sub> 0.38 (50% Hex/EtOAc)	1b, 1c

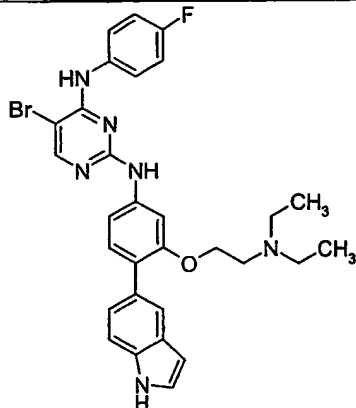
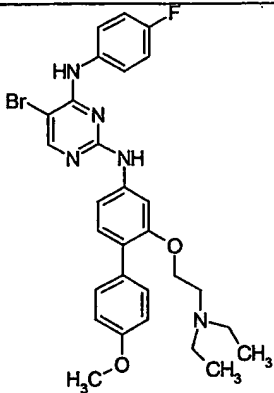
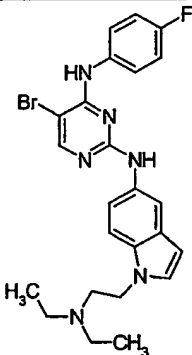
Example No.	Structures	Characterization <sup>a</sup>	Method
86		$(M+H)^+$ 356.1 RT 2.16 min TLC R <sub>f</sub> 0.80 (20% MeOH/CH <sub>2</sub> Cl <sub>2</sub> )	1b, 1c
87		$(M+H)^+$ 580.3 RT 2.43 min TLC R <sub>f</sub> 0.34 (9/1 CH <sub>2</sub> Cl <sub>2</sub> /MeOH)	B7a, B7b, N1, B7c, 1b, 1c
88		$(M+H)^+$ 499.1 RT 1.90 min TLC R <sub>f</sub> 0.35 (9/1 CH <sub>2</sub> Cl <sub>2</sub> /MeOH)	N8, N9, B7c, 1b, 1c
89		$(M+H)^+$ 504.4 RT 1.90 min TLC R <sub>f</sub> 0.27 (9/1 CH <sub>2</sub> Cl <sub>2</sub> /MeOH)	B7b, B7c, 1b, 1c

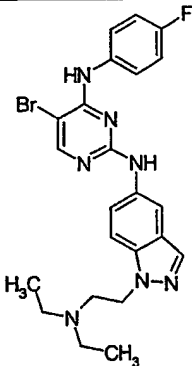
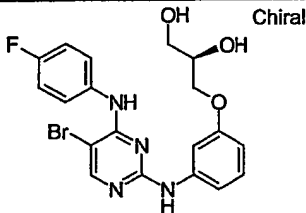
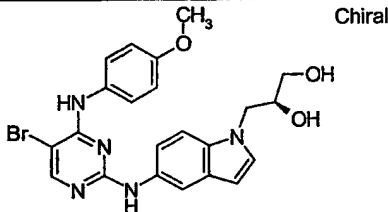
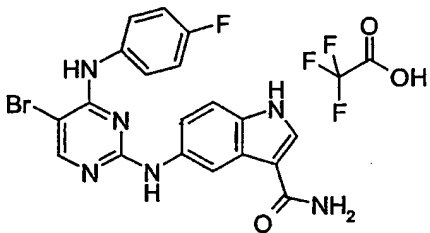
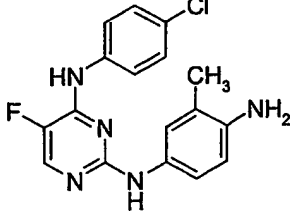
Example No.	Structures	Characterization <sup>a</sup>	Method
90		$(M+H)^+$ 418.0 RT 2.63 min TLC R <sub>f</sub> 0.0885 (20 % EtOAc/Hex)	1b, 1c
91		$(M+H)^+$ 432.0 RT 2.59min TLC R <sub>f</sub> 0.2678 (2% MeOH/CH <sub>2</sub> Cl <sub>2</sub> )	1b, 1c
92		$(M+H)^+$ 504.4 RT 1.94 min	N8, N9, B7c, 1b, 1c
93		$(M+H)^+$ 602.9 RT 2.17 min	B7a, B7b, N1, B7c, 1b, 1c

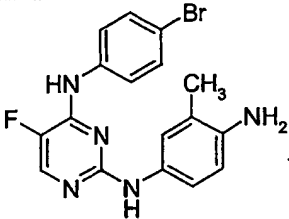
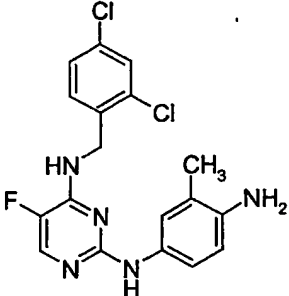
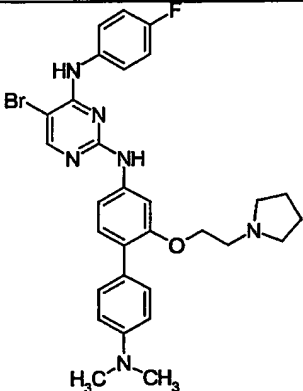
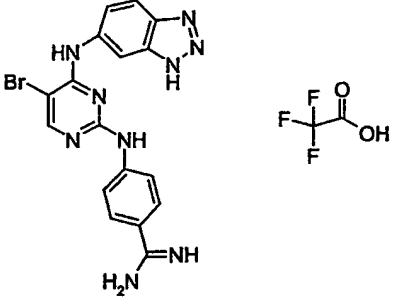
Example No.	Structures	Characterization <sup>a</sup>	Method
90		$(M+H)^+$ 418.0 RT 2.63 min TLC R <sub>f</sub> 0.0885 (20 % EtOAc/Hex)	1b, 1c
91		$(M+H)^+$ 432.0 RT 2.59 min TLC R <sub>f</sub> 0.2678 (2% MeOH/CH <sub>2</sub> Cl <sub>2</sub> )	1b, 1c
92		$(M+H)^+$ 504.4 RT 1.94 min	N8, N9, B7c, 1b, 1c
93		$(M+H)^+$ 602.9 RT 2.17 min	B7a, B7b, N1, B7c, 1b, 1c

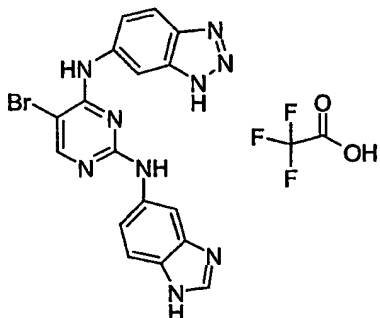
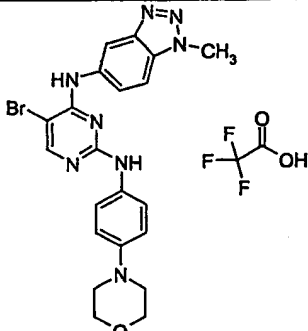
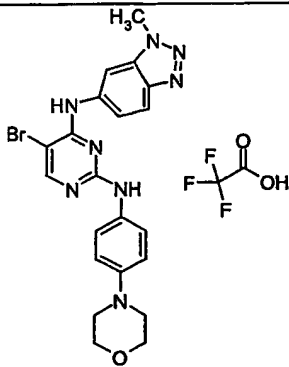
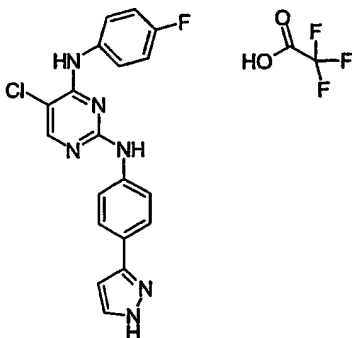


Example No.	Structures	Characterization <sup>a</sup>	Method
97		$(M+H)^+$ 520.0 RT 1.90 min TLC R <sub>f</sub> 0.27 (20/1 CH <sub>2</sub> Cl <sub>2</sub> /MeOH)	N8, N9, B7c, 1b, 1c
98		$(M+H)^+$ 429.2 RT 2.40 min	N6, B7c, 1b, 1c
99		$(M+H)^+$ 442.1 RT 2.21 min TLC R <sub>f</sub> 0.92 (10% MeOH/EtOAc)	1b, 1c
100		$(M+H)^+$ 485.1 RT 2.12 min TLC R <sub>f</sub> 0.92 (10% MeOH/EtOAc)	1b, 1c

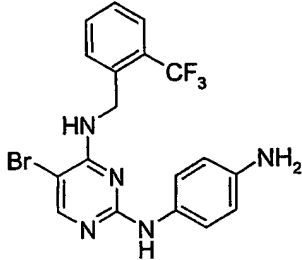
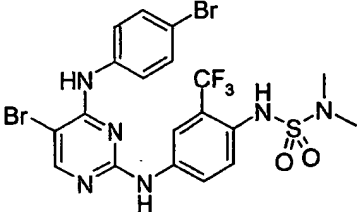
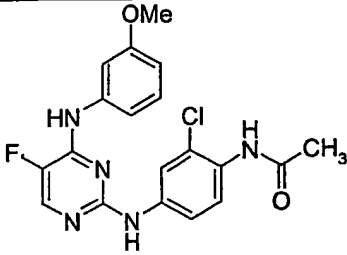
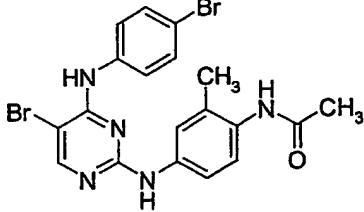
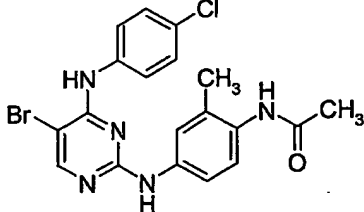
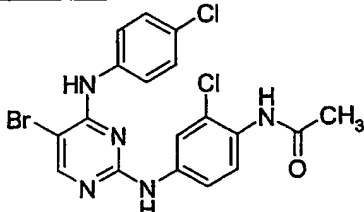
Example No.	Structures	Characterization <sup>a</sup>	Method
101		(M+H) <sup>+</sup> 591.2 RT 2.37 min TLC R <sub>f</sub> 0.28 (9/1 CH <sub>2</sub> Cl <sub>2</sub> /MeOH with 0.5% AmmOH)	B7a, B7b, N1, B7c, 1b, 1c
102		(M+H) <sup>+</sup> 582.2 RT 2.44 min	B7a, B7b, N1, B7c, 1b, 1c
103		(M+H) <sup>+</sup> 499.3 RT 1.87 min	N6, B7c, 1b, 1c

Example No.	Structures	Characterization <sup>a</sup>	Method
104		(M+H) <sup>+</sup> 500.2 RT 1.84 min	N6, B7c, 1b, 1c
105		(M+H) <sup>+</sup> 449.5 RT 2.11 min TLC R <sub>f</sub> 0.73 (20% MeOH/80% CHCl <sub>3</sub> ) mp = 168-169 °C	1b, 1c, 6
106		(M+H) <sup>+</sup> 484.4 RT 2.06 min TLC R <sub>f</sub> 0.24 (50% EtOAc/HEX)	4, B1, 1b, 1c
107		(M+H) <sup>+</sup> 441.1 RT 1.88 min TLC R <sub>f</sub> 0.73 (EtOAc)	1b, 1c
108		RT 233 (M+H) <sup>+</sup> 344.3	22, 23

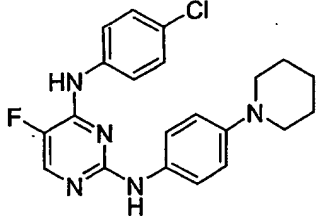
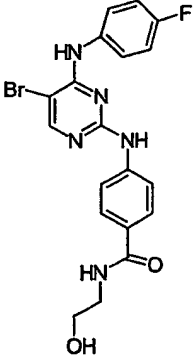
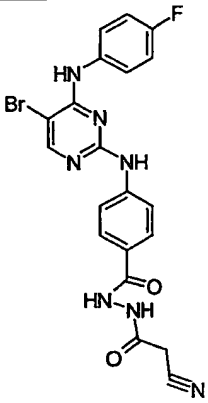
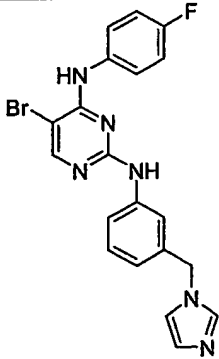
Example No.	Structures	Characterization <sup>a</sup>	Method
109		RT 2.33 (M+H) <sup>+</sup> 388.2	22, 23
110		RT 2.29 (M+H) <sup>+</sup> 392.2	22, 23
111		(M+H) <sup>+</sup> 594.4 RT 2.19 min	B7a, B7b, N1, B7c, 1b, 1c
112		(M+H) <sup>+</sup> 425.1 RT 1.87 min TLC R <sub>f</sub> 0.80 (10% MEOH/EtOAc)	1b, 1c

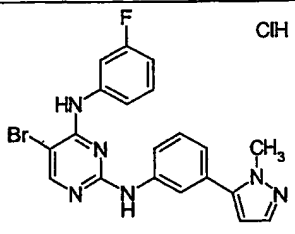
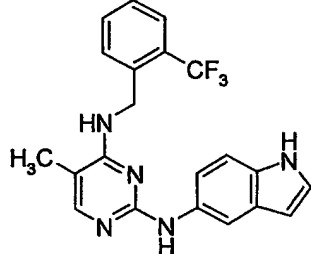
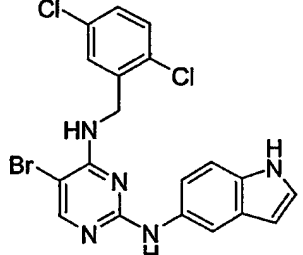
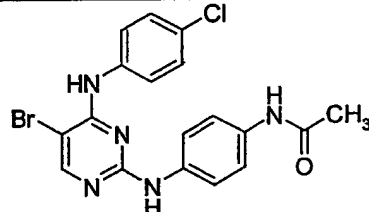
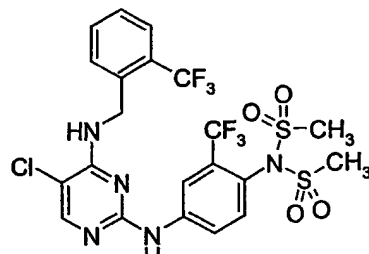
Example No.	Structures	Characterization <sup>a</sup>	Method
113		<p>(M+H)<sup>+</sup> 425.1 RT 1.87 min TLC R<sub>f</sub> 0.80 (10% MeOH/EtOAc)</p>	1b, 1c
114		<p>(M+H)<sup>+</sup> 485.1 RT 2.01 min TLC R<sub>f</sub> 0.88 (10% MeOH/EtOAc)</p>	1b, 1c
115		<p>(M+H)<sup>+</sup> 481.7 RT 2.07 min TLC R<sub>f</sub> 0.88 (10% MeOH/EtOAc)</p>	1b, 1c
116		<p>(M+H)<sup>+</sup> 381.4 RT 2.32 min TLC R<sub>f</sub> 0.76 (10% MeOH/HEX)</p>	B3, 1b, 1c

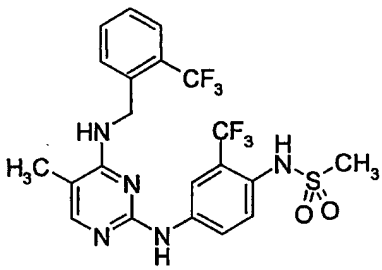
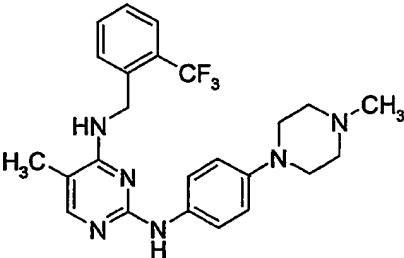
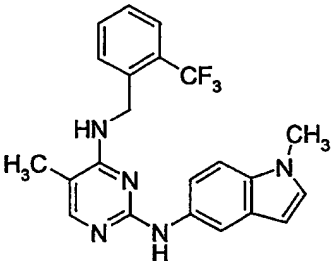
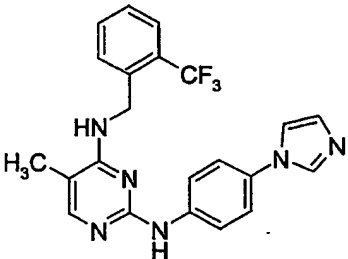
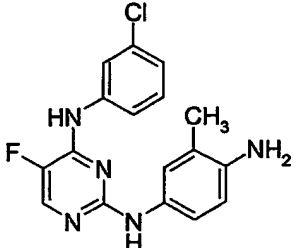
Example No.	Structures	Characterization <sup>a</sup>	Method
117		$(M+H)^+$ 421.4 RT 1.82 min TLC R <sub>f</sub> 0.77 (10% MEOH/EtOAc)	1b, 1c
118		$(M+H)^+$ 618.9 RT 2.75 min TLC R <sub>f</sub> 0.19 (95/5 CH <sub>2</sub> Cl <sub>2</sub> /MeOH)	B7a, B7b, N1, B7c, 1b, 1c
119		RT 1.96 $(M+H)^+$ 370.3	22
120		RT 1.98 $(M+H)^+$ 366.3	22
121		RT 1.98 $(M+H)^+$ 366.3	22

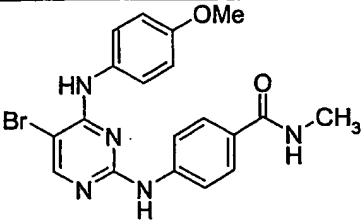
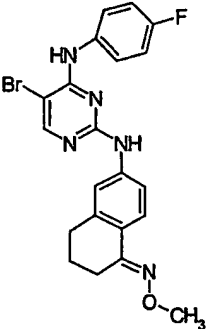
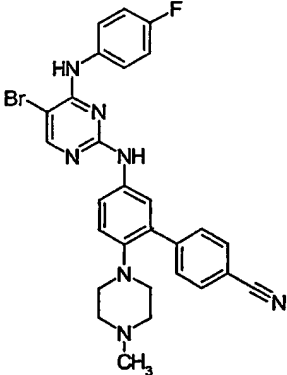
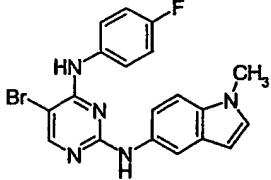
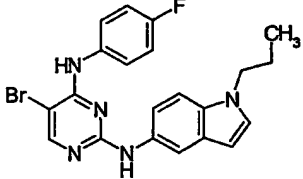
Example No.	Structures	Characterization <sup>a</sup>	Method
122		RT 2.34 (M+H) <sup>+</sup> 438.3	22, 23
123		RT 3.30 (M+H) <sup>+</sup> 608.8	22, 23, 26
124		RT 3.17 (M+H) <sup>+</sup> 402.2	22
125		RT 2.45 (M+H) <sup>+</sup> 490.1	22
126		RT 2.40 (M+H) <sup>+</sup> 446.2	22
127		RT 2.72 (M+H) <sup>+</sup> 466.1	22

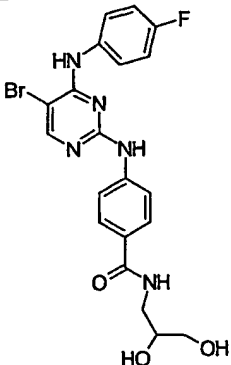
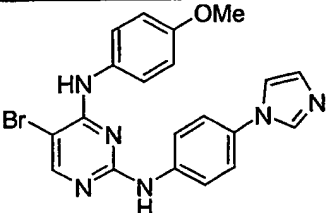
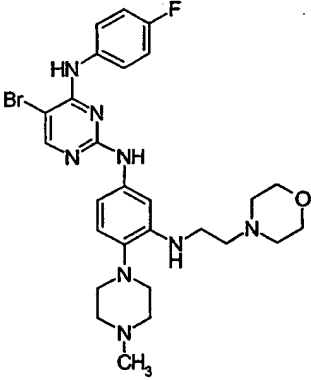
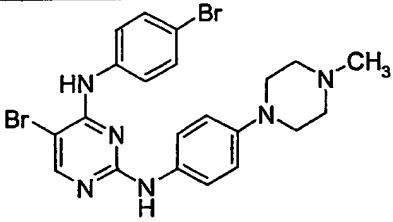
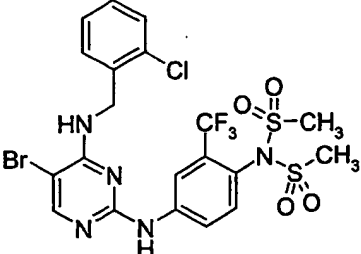
Example No.	Structures	Characterization <sup>a</sup>	Method
128		RT 1.42 (M+H) <sup>+</sup> 393.3	22
129		RT 1.66 (M+H) <sup>+</sup> 457.3	22
130		RT 1.46 (M+H) <sup>+</sup> 324.3	22, 23
131		RT 1.36 (M+H) <sup>+</sup> 328.2	22, 23
132		RT 2.92 (M+H) <sup>+</sup> 350.4	22
133		(M+H) <sup>+</sup> 441.2 RT 2.59 min TLC R <sub>f</sub> 0.29 (20% iPrOH/80% HEX)	B3, 1b, 1c

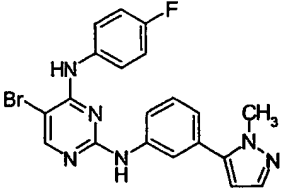
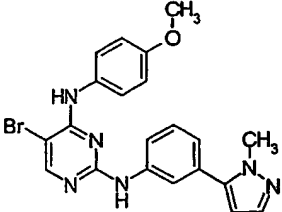
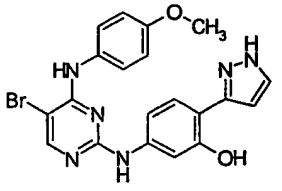
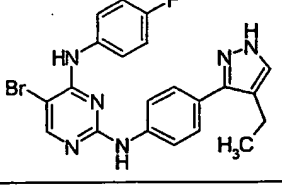
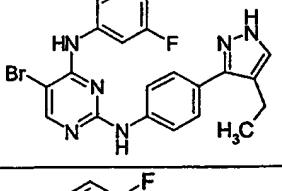
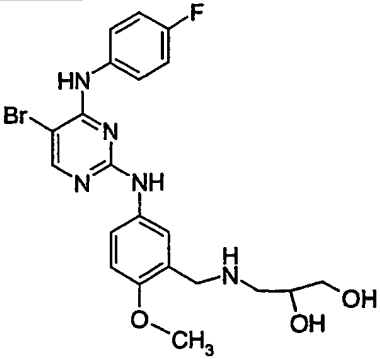
Example No.	Structures	Characterization <sup>a</sup>	Method
134		RT 2.01 (M+H) <sup>+</sup> 398.2	22
135		(M+H) <sup>+</sup> 446.6 RT 2.11 min TLC R <sub>f</sub> 0.56 (80% EtOAc/Hex)	1b, 1c, 17a, 17b
136		(M+H) <sup>+</sup> 448.0 RT 2.04 min TLC R <sub>f</sub> 0.70 (10% MeOH/EtOAc)	1b, 1c, 17a, 17b
137		(M+H) <sup>+</sup> 439.1 RT 1.91 min TLC R <sub>f</sub> 0.21 (95/5 CH <sub>2</sub> Cl <sub>2</sub> /MeOH)	N7, B7c, 1b, 1c

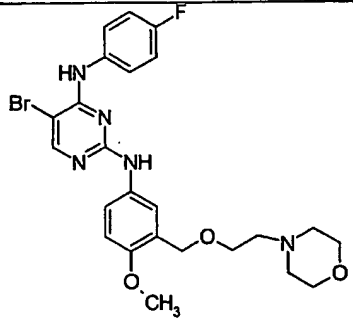
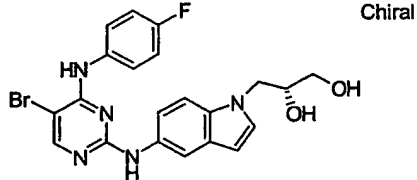
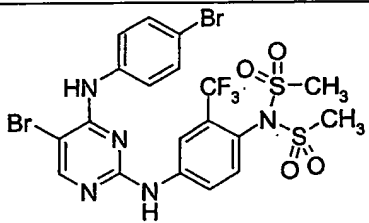
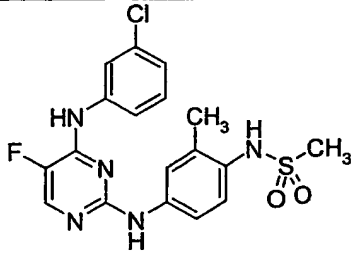
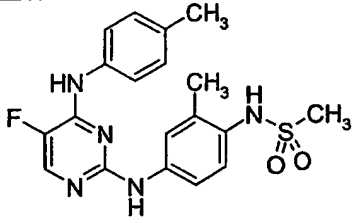
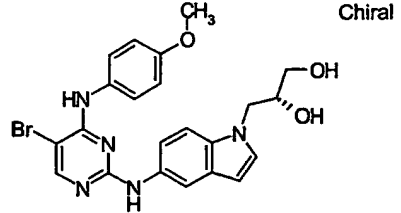
Example No.	Structures	Characterization <sup>a</sup>	Method
138	 <p>ClH</p>	$(M+H)^+$ 439.7 RT 2.76 min TLC R <sub>f</sub> 0.56 (20% iPrOH/80% HEX)	B3, 1b, 1c
139		RT 2.37 $(M+H)^+$ 398	22
140		RT 2.49 $(M+H)^+$ 462	22
141		RT 2.44 $(M+H)^+$ 432.2	22
142		RT 3.28 $(M+H)^+$ 618.0	22, 23, 25

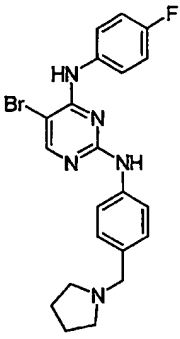
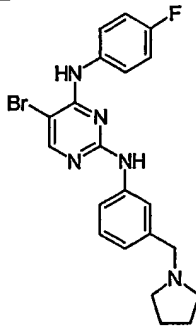
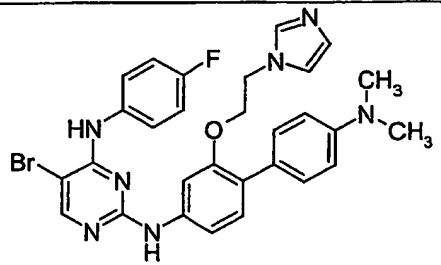
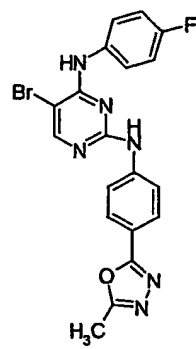
Example No.	Structures	Characterization <sup>a</sup>	Method
143		RT 2.35 (M+H) <sup>+</sup> 520.1	22, 23, 26
144		RT 1.63 (M+H) <sup>+</sup> 457.4	22
145		RT 2.56 (M+H) <sup>+</sup> 412.2	22
146		RT 1.64 (M+H) <sup>+</sup> 425.3	22
147		RT 1.64 (M+H) <sup>+</sup> 344.2	22, 23

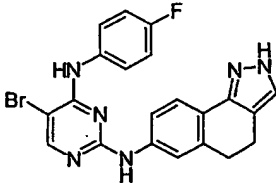
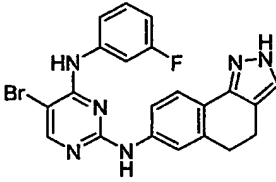
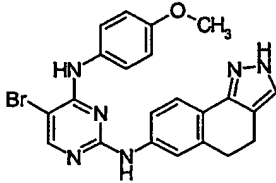
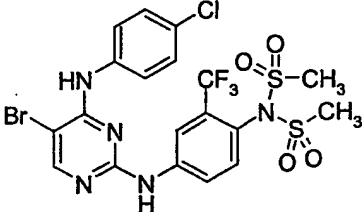
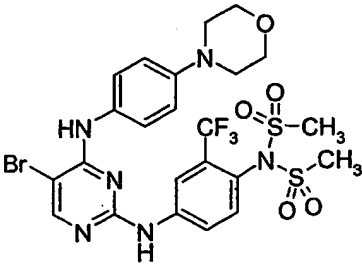
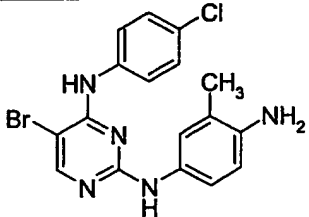
Example No.	Structures	Characterization <sup>a</sup>	Method
148		RT 2.10 (M+H) <sup>+</sup> 430.2	22
149		(M+H) <sup>+</sup> 456.0 RT 3.17 min TLC R <sub>f</sub> 0.78 (50% EtOAc/HEX)	1b, 1c, 7
150		(M+H) <sup>+</sup> 560.1 RT 2.21 min	N3, B7c, 1b, 1c
151		(M+H) <sup>+</sup> 414.2 RT 2.48 min TLC R <sub>f</sub> 0.62 (50% EtOAc/HEX) mp = 202 °C	B2B, 1b, 1c
152		(M+H) <sup>+</sup> 440.2 RT 2.74 min TLC R <sub>f</sub> 0.73 (50% EtOAc/HEX)	B2B, 1b, 1c

Example No.	Structures	Characterization <sup>a</sup>	Method
153		$(M+H)^+$ 476.6 RT 2.05 min TLC R <sub>f</sub> 0.56 (10% MeOH/EtOAc)	1b, 1c, 17a, 17b
154		RT 1.83 $(M+H)^+$ 437.5	22
155		$(M+H)^+$ 587.0 RT 1.35 min	N5, B7c, 1b, 1c
156		RT 0.43 $(M+H)^+$ 517.1	22
157		RT 3.24 $(M+H)^+$ 627.9	22, 23, 25

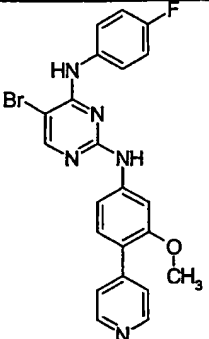
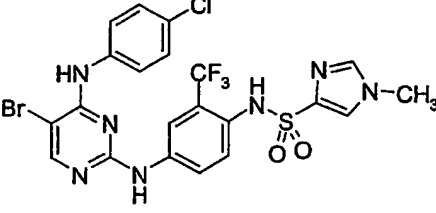
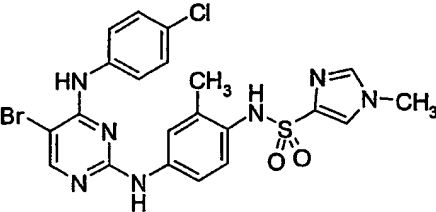
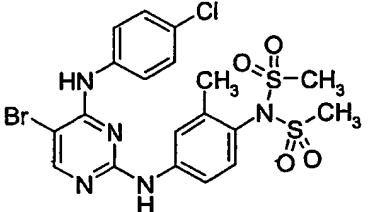
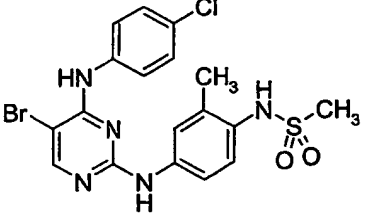
Example No.	Structures	Characterization <sup>a</sup>	Method
158		(M+H) <sup>+</sup> 439.3 RT 2.89 min TLC R <sub>f</sub> 0.52 (50% EtOAc/HEX)	B3, 1b, 1c
159		(M+H) <sup>+</sup> 451.6 RT 2.41 min TLC R <sub>f</sub> 0.52 (50% EtOAc/HEX)	B3, 1b, 1c
160		(M+H) <sup>+</sup> 453.2 RT 2.67 min TLC R <sub>f</sub> 0.45 (50% EtOAc/HEX)	B3, 1b, 1c
161		(M+H) <sup>+</sup> 453.3 RT 2.56 min TLC R <sub>f</sub> 0.63 (50% EtOAc/HEX)	B3, 1b, 1c
162		(M+H) <sup>+</sup> 453.3 RT 2.73 min TLC R <sub>f</sub> 0.68 (EtOAc)	B3, 1b, 1c
163		(M+H) <sup>+</sup> 492.2 RT 1.71 min TLC R <sub>f</sub> 0.15 (20% MeOH/CH <sub>2</sub> Cl <sub>2</sub> )	N8, N9, B7c, 1b, 1c

Example No.	Structures	Characterization <sup>a</sup>	Method
164		$(M+H)^+$ 532.0 RT 1.92 min TLC R <sub>f</sub> 0.74 (100% EtOAc)	N8, N9, B7c, 1b, 1c
165		$(M+H)^+$ 472.3 RT 2.03 min TLC R <sub>f</sub> 0.36 (50% EtOAc/HEX)	B1, 1b, 1c, 10
166		RT 3.95 $(M+H)^+$ 657.8	22, 23, 25
167		RT 2.69 $(M+H)^+$ 422.2	22, 23, 26
168		RT 2.15 $(M+H)^+$ 402.2	22, 23, 26
169		$(M+H)^+$ 486.3 RT 2.06 min TLC R <sub>f</sub> 0.24 (50% EtOAc/HEX)	B1, 1b, 1c

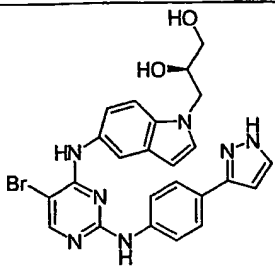
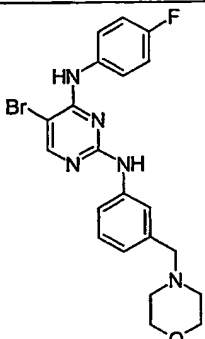
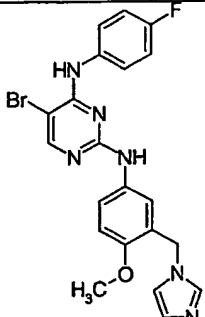
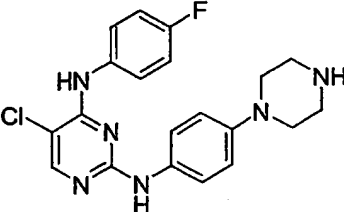
Example No.	Structures	Characterization <sup>a</sup>	Method
170		$(M+H)^+$ 441.9 RT 1.86 min TLC R <sub>f</sub> 0.35 (95/5 CH <sub>2</sub> Cl <sub>2</sub> /MeOH with 0.5% NH <sub>4</sub> OH)	N7, B7c, 1b, 1c
171		$(M+H)^+$ 442.1 RT 1.96 min TLC R <sub>f</sub> 0.25 (85/15 CH <sub>2</sub> Cl <sub>2</sub> /MeOH)	N7, B7c, 1b, 1c
172		$(M+H)^+$ 588.2 RT 2.11 min TLC R <sub>f</sub> 0.08 (50% Hex/EtOAc)	B7c, 1b, 1c
173		$(M+H)^+$ 441.2 RT 2.59 min TLC R <sub>f</sub> 0.75 (80% EtOAc/HEX)	1b, 1c, 17a, 17b, 18

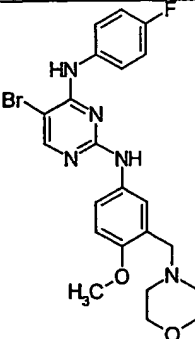
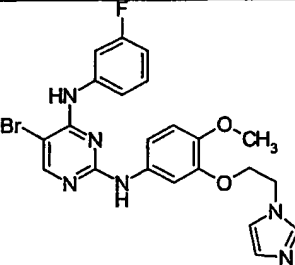
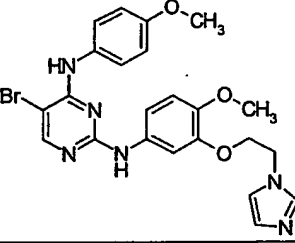
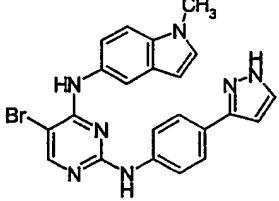
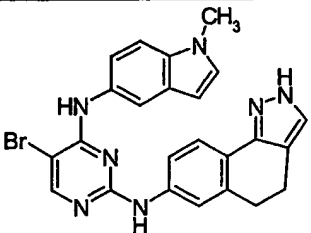
Example No.	Structures	Characterization <sup>a</sup>	Method
174		(M+H) <sup>+</sup> 451.3 RT 2.36 min TLC R <sub>f</sub> 0.67 (EtOAc)	B3, 1b, 1c
175		(M+H) <sup>+</sup> 451.3 RT 2.66 min TLC R <sub>f</sub> 0.70 (EtOAc)	B3, 1b, 1c
176		(M+H) <sup>+</sup> 463.3 RT 2.27 min TLC R <sub>f</sub> 0.64 (EtOAc)	B3, 1b, 1c
177		RT 3.43 (M+H) <sup>+</sup> 614.0	22, 23, 25
178		RT 2.90 (M+H) <sup>+</sup> 665.1	22, 23, 25
179		RT 1.94 (M+H) <sup>+</sup> 404.3	22, 23

Example No.	Structures	Characterization <sup>a</sup>	Method
180		RT 2.28 (M+H) <sup>+</sup> 422.2	22, 23, 26
181		RT 2.71 (M+H) <sup>+</sup> 500.1	22, 23, 25
182		RT 3.15 (M+H) <sup>+</sup> 628.0	22, 23, 25
183		(M+H) <sup>+</sup> 438.9 RT 1.82 min TLC R <sub>f</sub> 0.54 (85/15 CH <sub>2</sub> Cl <sub>2</sub> /MeOH)	N7, B7c, 1b, 1c
184		RT 2.48 (M+H) <sup>+</sup> 456.2	22, 23, 26

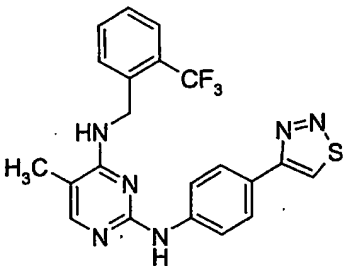
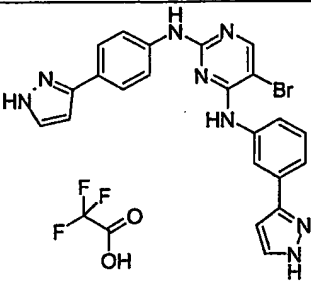
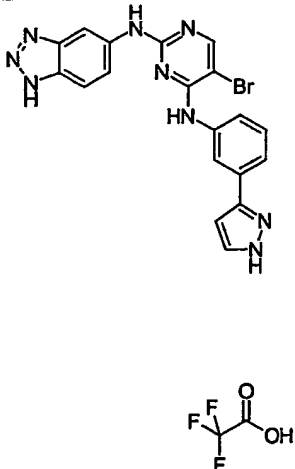
Example No.	Structures	Characterization <sup>a</sup>	Method
185		$(M+H)^+$ 468.3 RT 2.26 min TLC R <sub>f</sub> 0.40 (95/5 CH <sub>2</sub> Cl <sub>2</sub> /MeOH with 0.5% AmmOH)	N2, B7c, 1b, 1c
186		RT 2.89 $(M+H)^+$ 602.0	22, 23, 26
187		RT 2.49 $(M+H)^+$ 548.0	22, 23, 26
188		RT 2.91 $(M+H)^+$ 560.1	22, 23, 25
189		RT 2.49 $(M+H)^+$ 482.1	22, 23, 26

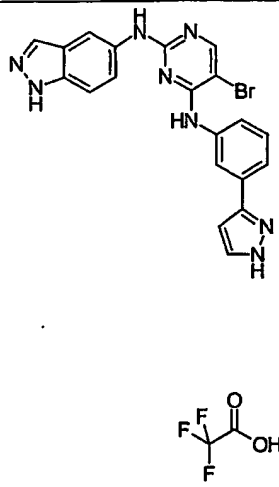
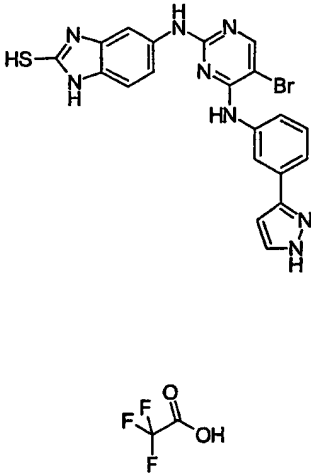
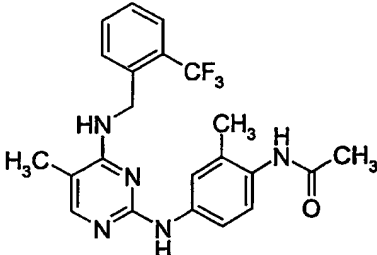
Example No.	Structures	Characterization <sup>a</sup>	Method
190		$(M+H)^+$ 579.2 RT 2.06 min TLC R <sub>f</sub> 0.30 (9/1 CH <sub>2</sub> Cl <sub>2</sub> /MeOH)	N3, B7c, 1b, 1c
191		RT 3.40 $(M+H)^+$ 588.0/590.0	22, 23, 25
192		RT 2.93 $(M+H)^+$ 680	22, 23, 26
193		RT 2.13 $(M+H)^+$ 441.3	22, 27
194		RT 1.56 $(M+H)^+$ 443.3	22

Example No.	Structures	Characterization <sup>a</sup>	Method
195	 <p>Chiral</p>	$(M+H)^+$ 520.4 RT 2.02 min TLC R <sub>f</sub> 0.48 (10% MeOH/90% EtOAc)	B3, B1, 1b, 1c
196		$(M+H)^+$ 458.1 RT 1.86 min TLC R <sub>f</sub> 0.56 (95/5 CH <sub>2</sub> Cl <sub>2</sub> /MeOH)	N7, B7c, 1b, 1c
197		$(M+H)^+$ 468.9 RT 1.85 min TLC R <sub>f</sub> 0.36 (9/1 CH <sub>2</sub> Cl <sub>2</sub> /MeOH)	B7b, B7c, 1b, 1c
198		RT 1.33 $(M+H)^+$ 399.2	22

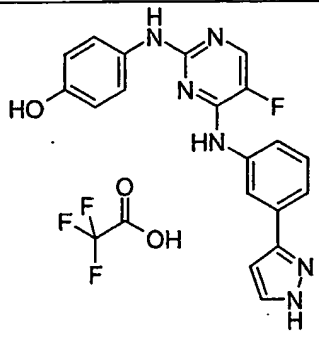
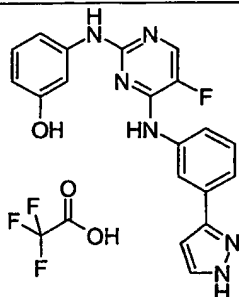
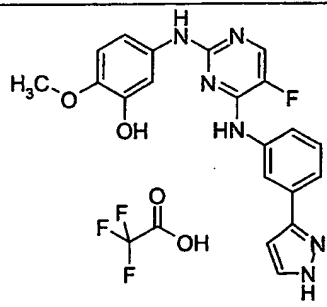
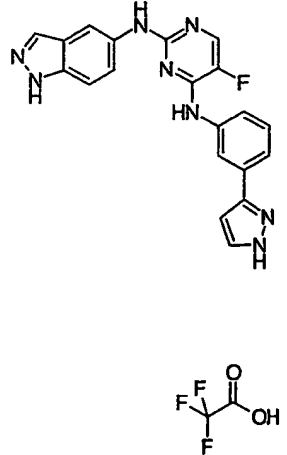
Example No.	Structures	Characterization <sup>a</sup>	Method
199		$(M+H)^+$ 490.0 RT 2.29 min TLC R <sub>f</sub> 0.21 (95/5 CH <sub>2</sub> Cl <sub>2</sub> /MeOH)	B7b, B7c, 1b, 1c
200		$(M+H)^+$ 499.2 RT 2.01 min TLC R <sub>f</sub> 0.53 (20% MeOH/80% EtOAc)	N8, N9, B7c, 1b, 1c
201		$(M+H)^+$ 511.1 RT 1.81 min TLC R <sub>f</sub> 0.46 (20% MeOH/80% EtOAc)	N8, N9, B7c, 1b, 1c
202		$(M+H)^+$ 460.2 RT 2.80 min TLC R <sub>f</sub> 0.46 (EtOAc)	B3, 8, 1b, 1c
203		$(M+H)^+$ 486.3 RT 2.33 min TLC R <sub>f</sub> 0.65 (EtOAc)	B3, 9, 1b, 1c

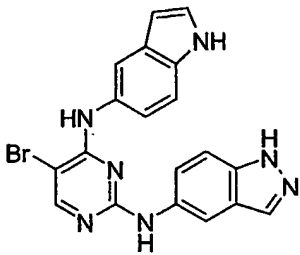
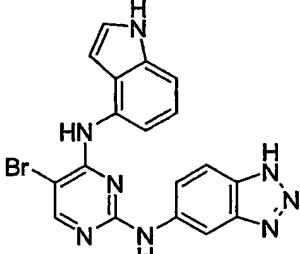
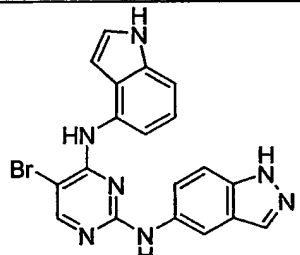
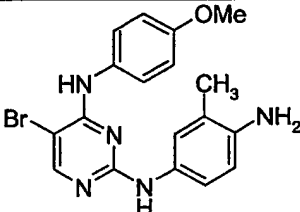
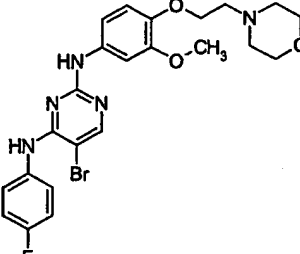
Example No.	Structures	Characterization <sup>a</sup>	Method
204		RT 1.74 (M+H) <sup>+</sup> 427.3/429.2	22
205		(M+H) <sup>+</sup> 459.0 RT 2.01 min TLC R <sub>f</sub> 0.14 (EtOAc)	1b, 1c, 17a, 17b
206	<p>Chiral</p>	(M+H) <sup>+</sup> 456.3 RT 2.55 min TLC R <sub>f</sub> 0.63 (50% Hex/EtOAc)	B6, 1b, 1c
207	<p>Chiral</p>	(M+H) <sup>+</sup> 476.2 RT 2.30 min TLC R <sub>f</sub> 0.35 (50% Hex/EtOAc)	1b, 1c
208		RT 2.31 (M+H) <sup>+</sup> 521.2	22, 23, 26

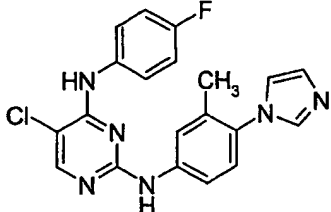
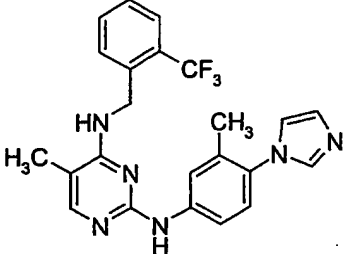
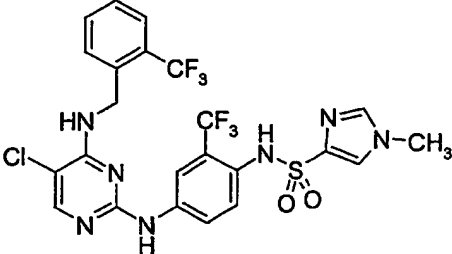
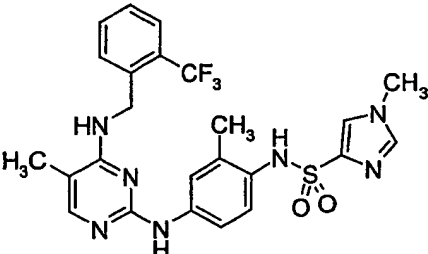
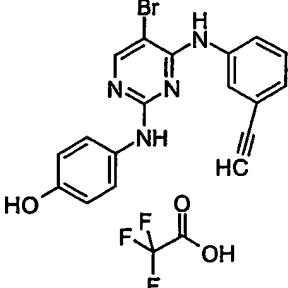
Example No.	Structures	Characterization <sup>a</sup>	Method
209		RT 2.49 (M+H) <sup>+</sup> 443.1	22
210		(M+H) <sup>+</sup> 473.4 RT 2.13 min TLC R <sub>f</sub> 0.34 (100% EtOAc)	B3, 1b, 1d
211		(M+H) <sup>+</sup> 448.1 RT 2.09 min TLC R <sub>f</sub> 0.39 (100% EtOAc)	1b, 1d

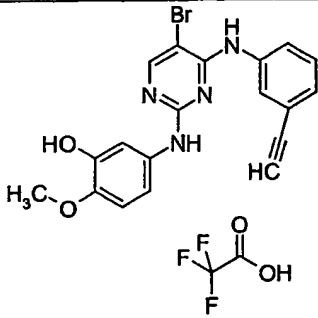
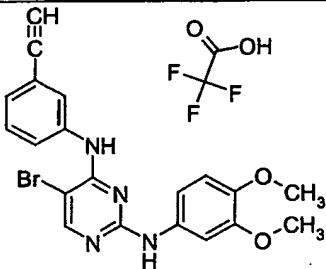
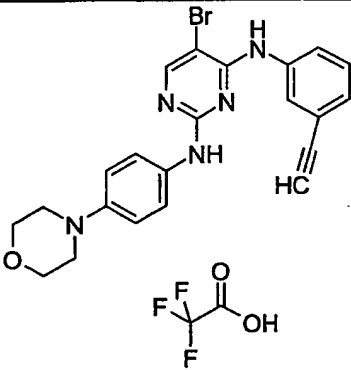
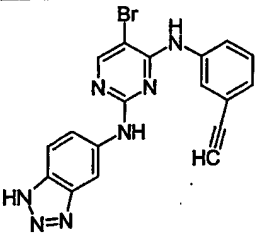
Example No.	Structures	Characterization <sup>a</sup>	Method
212	 <p>The structure shows a pyrazole ring substituted with a 4-(4-bromo-2-((1H-indol-3-ylideneamino)amino)phenylamino)phenyl group. Below it is the trifluoroacetic acid (TFA) salt structure: <chem>CC(F)(F)C(=O)O</chem>.</p>	(M+H) <sup>+</sup> 447.3 RT 2.02 min TLC R <sub>f</sub> 0.30 (100% EtOAc)	1b, 1d
213	 <p>The structure shows a pyrazole ring substituted with a 4-(4-bromo-2-((1H-indol-3-ylideneamino)amino)phenylamino)phenyl group and a thiol (-SH) group. Below it is the trifluoroacetic acid (TFA) salt structure: <chem>CC(F)(F)C(=O)O</chem>.</p>	(M+H) <sup>+</sup> 479.3 RT 1.98 min TLC R <sub>f</sub> 0.31 (100% EtOAc)	1b, 1d
214	 <p>The structure shows a pyrazole ring substituted with a 4-(4-(trifluoromethyl)phenylamino)phenyl group and a 4-(4-(acetamido)phenylamino)phenyl group. The trifluoromethyl group is represented as CF<sub>3</sub>.</p>	RT 2.10 (M+H) <sup>+</sup> 430.3	22

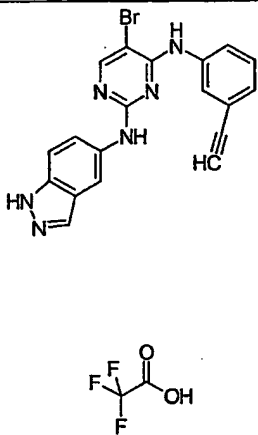
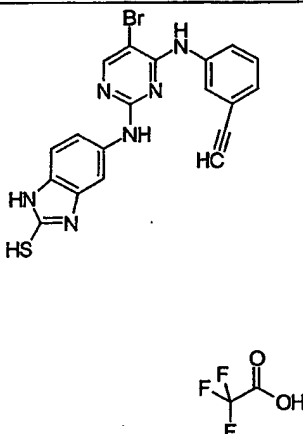
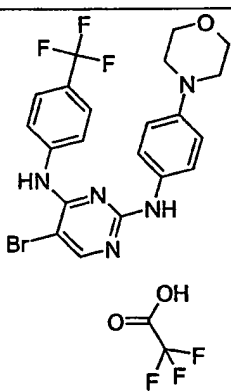
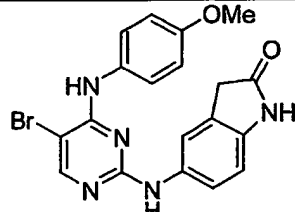
Example No.	Structures	Characterization <sup>a</sup>	Method
215		RT 1.72 (M+H) <sup>+</sup> 388.3	22, 23
216		(M+H) <sup>+</sup> 504.3 RT 2.57 min TLC R <sub>f</sub> 0.52 (70% EtOAc/Hex)	1b, 1c
217		(M+H) <sup>+</sup> 477.2 RT 2.66 min TLC R <sub>f</sub> 0.40 (EtOAc)	B4, 1b, 1c
218		(M+H) <sup>+</sup> 463.1 RT 2.40 min TLC R <sub>f</sub> 0.67 (20% MeOH/80% EtOAc)	B4, 1b, 1c, 8
219		(M+H) <sup>+</sup> 530.2 RT 1.92 min TLC R <sub>f</sub> 0.13 (20% MeOH/80% C HCl <sub>3</sub> )	N8, N9, B7c, 1b, 1c

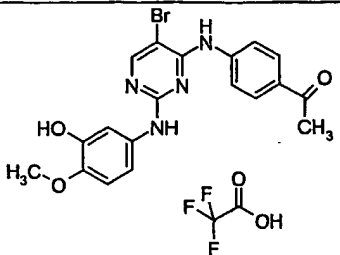
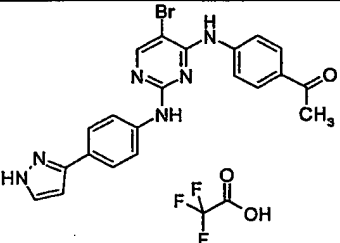
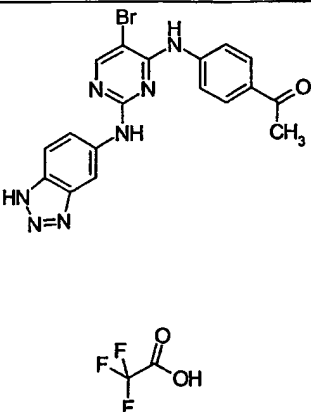
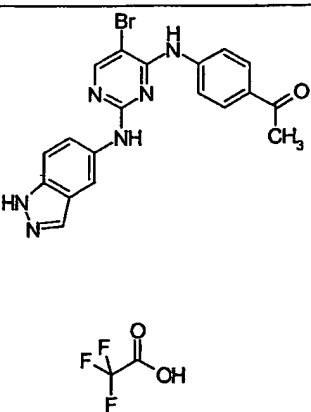
Example No.	Structures	Characterization <sup>a</sup>	Method
220		(M+H) <sup>+</sup> 363.3 RT 1.83 min TLC R <sub>f</sub> 0.60 (100% EtOAc)	1b, 1d
221		(M+H) <sup>+</sup> 363.3 RT 1.93 min TLC R <sub>f</sub> 0.66 (100% EtOAc)	1b, 1d
222		(M+H) <sup>+</sup> 393.3 RT 1.9 min TLC R <sub>f</sub> 0.58 (100% EtOAc)	1b, 1d
223		(M+H) <sup>+</sup> 387.3 RT 1.81 min TLC R <sub>f</sub> 0.25 (100% EtOAc)	1b, 1d

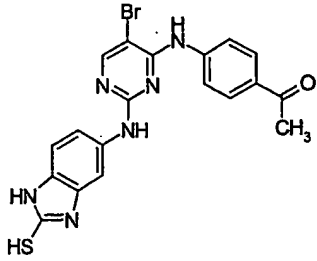
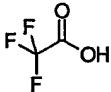
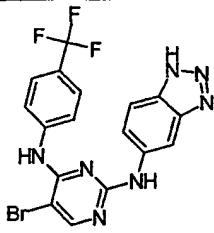
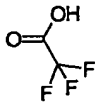
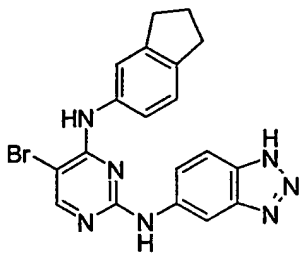
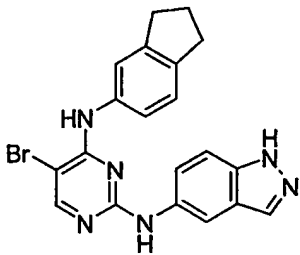
Example No.	Structures	Characterization <sup>a</sup>	Method
224		(M+H) <sup>+</sup> 420.3 RT 2.01 min TLC R <sub>f</sub> 0.46 (100% EtOAc)	1b, 1d
225		(M+H) <sup>+</sup> 421.2 RT 2.05 min TLC R <sub>f</sub> 0.71 (100% EtOAc)	1b, 1d
226		(M+H) <sup>+</sup> 420.3 RT 2.00 min TLC R <sub>f</sub> 0.66 (100% EtOAc)	1b, 1d
227		RT 1.70 (M+H) <sup>+</sup> 400.3/402.2	22, 23
228		(M+H) <sup>+</sup> 518.3 RT 1.76 min TLC R <sub>f</sub> 0.24 (50% EtOAc/HEX) mp = 100-101 °C	N8, N9, B7c, 1b, 1c

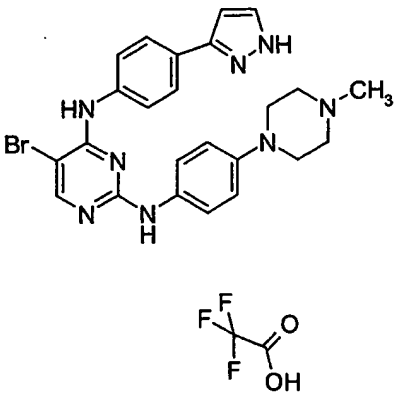
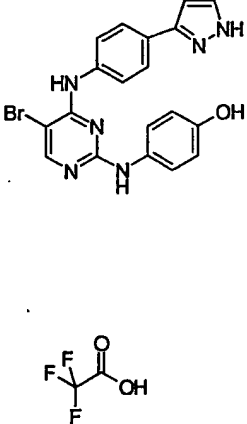
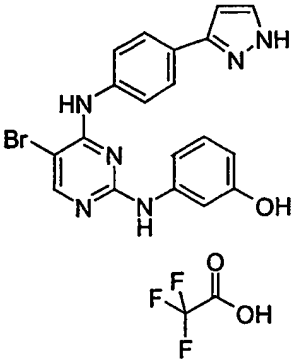
Example No.	Structures	Characterization <sup>a</sup>	Method
229		RT 1.92 (M+H) <sup>+</sup> 395.3	28, 22
230		RT 1.77 (M+H) <sup>+</sup> 439.3	28, 22
231		RT 2.70 (M+H) <sup>+</sup> 606.0	22, 23, 26
232		RT 2.15 (M+H) <sup>+</sup> 532.1	22, 23, 26
233		(M+H) <sup>+</sup> 381.3 RT 2.13 min TLC R <sub>f</sub> 0.89 (100% EtOAc)	1b, 1d

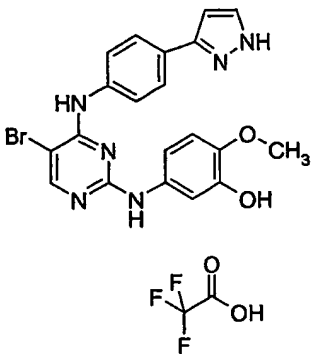
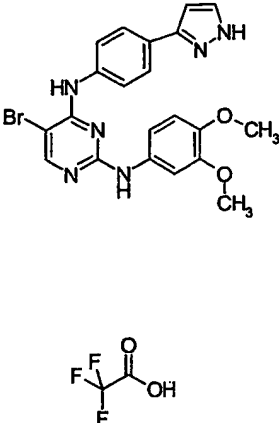
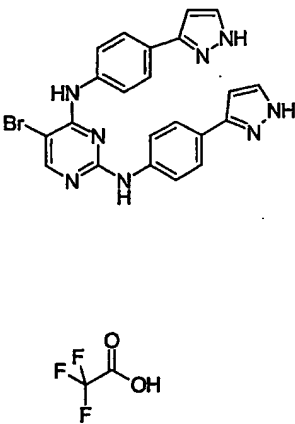
Example No.	Structures	Characterization <sup>a</sup>	Method
234		(M+H) <sup>+</sup> 411.3 RT 2.29 min TLC R <sub>f</sub> 0.87 (100% EtOAc)	1b, 1d
235		(M+H) <sup>+</sup> 425.3 RT 2.47 min TLC R <sub>f</sub> 0.85 (100% EtOAc)	1b, 1d
236		(M+H) <sup>+</sup> 450.3 RT 2.39min TLC R <sub>f</sub> 0.79 (100% EtOAc)	1b, 1d
237		(M+H) <sup>+</sup> 406.1 RT 2.27 min TLC R <sub>f</sub> 0.76 (100% EtOAc)	1b, 1d

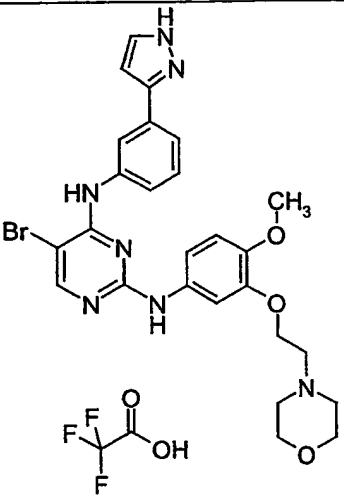
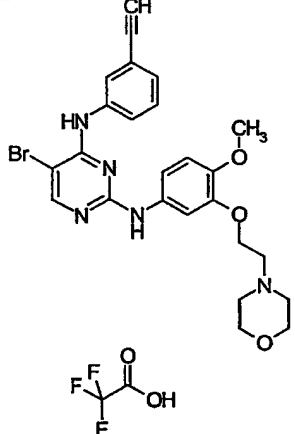
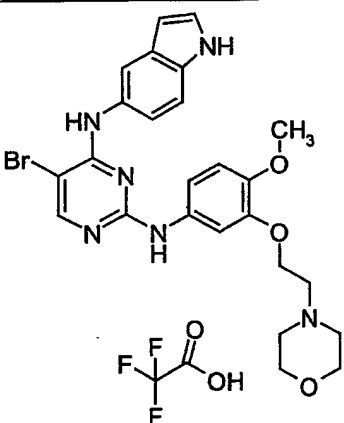
Example No.	Structures	Characterization <sup>a</sup>	Method
238		$(M+H)^+$ 407.2 RT 2.23 min TLC R <sub>f</sub> 0.73 (100% EtOAc)	1b, 1d
239		$(M+H)^+$ 439.1 RT 2.13 min TLC R <sub>f</sub> 0.68 (100% EtOAc)	1b, 1d
240		$(M+H)^+$ 494.2 RT 3.21min TLC R <sub>f</sub> 0.6475 (50% EtOAc/Hex)	1b, 1c
241		RT 1.90 $(M+H)^+$ 426.3/428.2	22

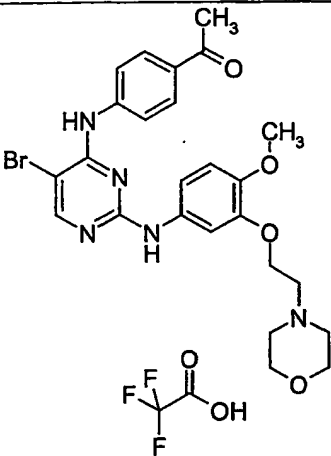
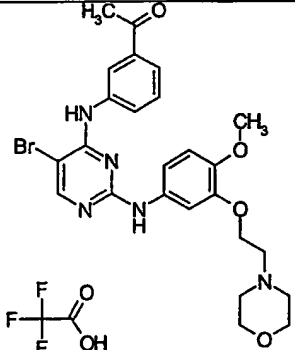
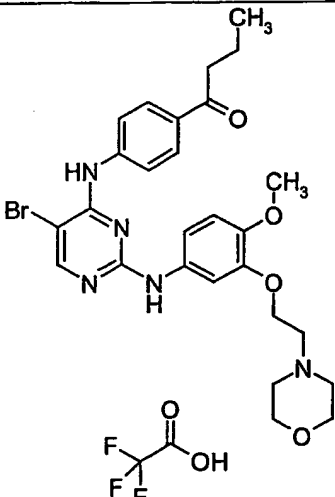
Example No.	Structures	Characterization <sup>a</sup>	Method
242		(M+H) <sup>+</sup> 429.3 RT 2.17 min TLC R <sub>f</sub> 0.84 (100% EtOAc)	1b, 1d
243		(M+H) <sup>+</sup> 468.3 RT 2.27 min TLC R <sub>f</sub> 0.63 (100% EtOAc)	B3, 1b, 1d
244		(M+H) <sup>+</sup> 424.4 RT 2.25 min TLC R <sub>f</sub> 0.66 (100% EtOAc)	1b, 1d
245		(M+H) <sup>+</sup> 423.2 RT 2.61 min TLC R <sub>f</sub> 0.86 (100% EtOAc)	1b, 1d

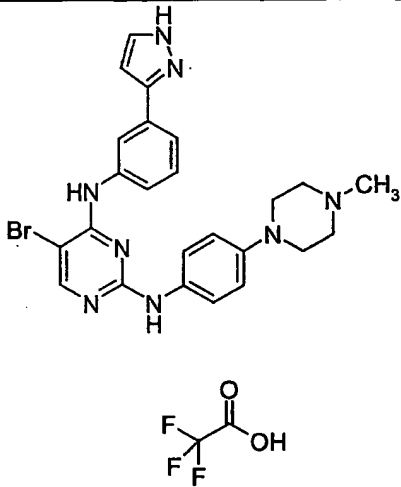
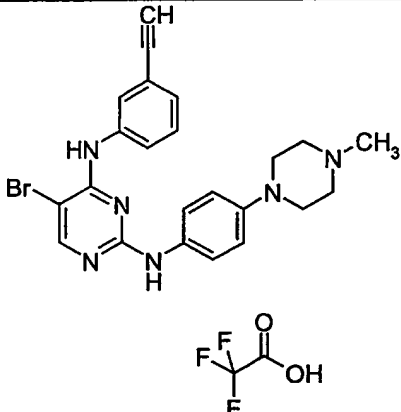
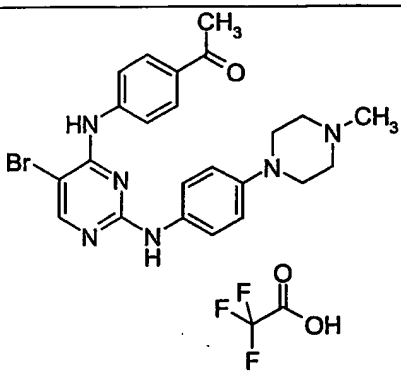
Example No.	Structures	Characterization <sup>a</sup>	Method
246	 	$(M+H)^+$ 455.2 RT 2.10 min TLC R <sub>f</sub> 0.73 (100% EtOAc)	1b, 1d
247	 	$((M+H)^+)$ 450.2/452.1 RT 2.73 min TLC R <sub>f</sub> 0.5312 (50% EtOAc/Hex)	1b, 1c
248		$(M+H)^+$ 422.3 RT 2.41 min TLC R <sub>f</sub> 0.49 (100% EtOAc)	1b, 1d
249		$(M+H)^+$ 421.4 RT 2.31 min TLC R <sub>f</sub> 0.53 (100% EtOAc)	1b, 1d

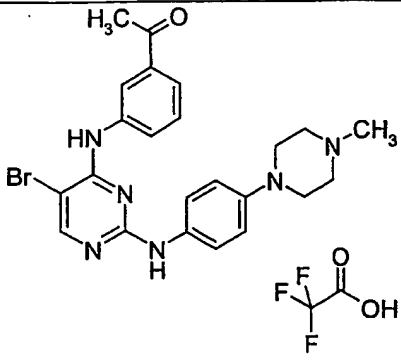
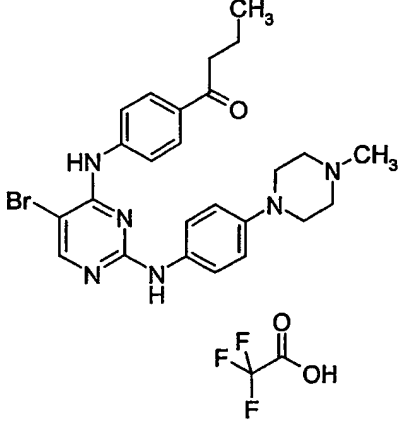
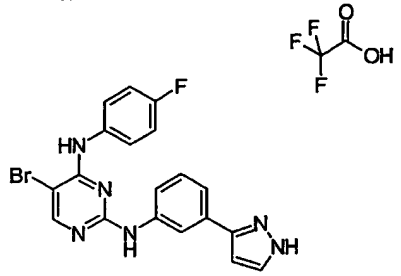
Example No.	Structures	Characterization <sup>a</sup>	Method
250		(M+H) <sup>+</sup> 505.4 RT 1.75 min TLC R <sub>f</sub> 0.063 (100% EtOAc)	B3, 1b, 1d
251		(M+H) <sup>+</sup> 423.4 RT 2.00 min TLC R <sub>f</sub> 0.25 (100% EtOAc)	B3, 1b, 1d
252		(M+H) <sup>+</sup> 423.4 RT 2.1 min TLC R <sub>f</sub> 0.31 (100% EtOAc)	B3, 1b, 1d

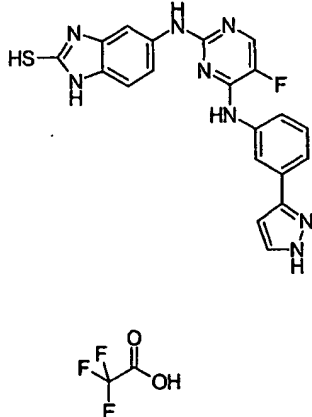
Example No.	Structures	Characterization <sup>a</sup>	Method
253		(M+H) <sup>+</sup> 453.3 RT 2.04 min TLC R <sub>f</sub> 0.19 (100% EtOAc)	B3, 1b, 1d
254		(M+H) <sup>+</sup> 467.4 RT 2.17 min TLC R <sub>f</sub> 0.40 (100% EtOAc)	B3, 1b, 1d
255		(M+H) <sup>+</sup> 473.4 RT 2.26 min TLC R <sub>f</sub> 0.21 (100% EtOAc)	B3, 1b, 1d

Example No.	Structures	Characterization <sup>a</sup>	Method
256		(M+H) <sup>+</sup> 566.2 RT 1.78 min TLC R <sub>f</sub> 0.28 (100% EtOAc)	N8, N9, B7c, 1b, 1d
257		(M+H) <sup>+</sup> 524.1 RT 2.00 min TLC R <sub>f</sub> 0.30 (100% EtOAc)	N8, N9, B7c, 1b, 1d
258		(M+H) <sup>+</sup> 541.1 RT 1.74 min TLC R <sub>f</sub> 0.30 (100% EtOAc)	N8, N9, B7c, 1b, 1d

Example No.	Structures	Characterization <sup>a</sup>	Method
259		(M+H) <sup>+</sup> 542.2 RT 1.92 min TLC R <sub>f</sub> 0.31 (100% EtOAc)	N8, N9, B7c, 1b, 1d
260		(M+H) <sup>+</sup> 542.1 RT 1.79 min TLC R <sub>f</sub> 0.28 (100% EtOAc)	N8, N9, B7c, 1b, 1d
261		(M+H) <sup>+</sup> 572.1 RT 2.18 min TLC R <sub>f</sub> 0.43 (100% EtOAc)	N8, N9, B7c, 1b, 1d

Example No.	Structures	Characterization <sup>a</sup>	Method
262	 <chem>Brc1nc(Nc2ccc(cc2)N3C=CN=C3)c(Nc4ccc(cc4)N5CCN(C)CC5)c1</chem> <chem>FC(F)(F)C(=O)O</chem>	(M+H) <sup>+</sup> 507.2 RT 1.60 min TLC R <sub>f</sub> 0.12 (100% EtOAc)	1b, 1d
263	 <chem>Brc1nc(Nc2ccc(cc2)C#C)c(Nc3ccc(cc3)N4CCN(C)CC4)c1</chem> <chem>FC(F)(F)C(=O)O</chem>	(M+H) <sup>+</sup> 463.2 RT 1.80 min TLC R <sub>f</sub> 0.23 (100% EtOAc)	1b, 1d
264	 <chem>Brc1nc(Nc2ccc(cc2)C(=O)C)c(Nc3ccc(cc3)N4CCN(C)CC4)c1</chem> <chem>FC(F)(F)C(=O)O</chem>	(M+H) <sup>+</sup> 481.2 RT 1.74 min TLC R <sub>f</sub> 0.21 (100% EtOAc)	1b, 1d

Example No.	Structures	Characterization <sup>a</sup>	Method
265		(M+H) <sup>+</sup> 481.2 RT 1.55 min TLC R <sub>f</sub> 0.24 (100% EtOAc)	1b, 1d
266		(M+H) <sup>+</sup> 511.2 RT 2.02 min TLC R <sub>f</sub> 0.23 (100% EtOAc)	1b, 1d
267		(M+H) <sup>+</sup> 425.4 RT 2.36 min TLC R <sub>f</sub> 0.40 (1% TFA/9% MeOH/90% CH <sub>2</sub> Cl <sub>2</sub> )	1b, 1c

Example No.	Structures	Characterization <sup>a</sup>	Method
268		(M+H) <sup>+</sup> 419.3 RT 1.71 min TLC R <sub>f</sub> 0.22 (100% EtOAc)	1b, 1d

<sup>a</sup> LC/MS method used: HPLC - electrospray mass spectra (HPLC ES-MS) for characterization were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluants were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flow rate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

The structure of each compound in Table 1 is consistent with the analytical data (<sup>1</sup>H NMR and LC-MS) also presented in the table above.

Table 2

## IUPAC Names of Compound Examples

Example No.	IUPAC Name*
1	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[3-(1-methyl-1 <i>H</i> -pyrazol-3-yl)phenyl]amine hydrochloride
2	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[3-(1 <i>H</i> -pyrazol-3-yl)phenyl]amine
3	(1 <i>E</i> )-1-[4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino) phenyl]ethanone oxime
4	<i>N</i> -{5-bromo-2-[(4-[(4 <i>R</i> )-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy)phenyl]amino]-4-pyrimidinyl}- <i>N</i> -(4-fluorophenyl)amine
5	2 <i>S</i> )-3-[4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenoxy]-1,2-propanediol

Example No.	IUPAC Name*
6	(2S)-3-[3-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenoxy]-1,2-propanediol
8	4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2-(2-hydroxyethoxy)benzoic acid
9	5-bromo- <i>N</i> <sup>2</sup> -(1-[[{(4 <i>R</i> )-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-1 <i>H</i> -indol-5-yl]- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine
10	(2S)-3-[5-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-1 <i>H</i> -indol-1-yl]-1,2-propanediol
13	5-bromo- <i>N</i> <sup>2</sup> -(4-[[{(4 <i>R</i> )-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}phenyl]- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine
14	(2 <i>R</i> )-3-[4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenoxy]-1,2-propanediol
15	5-bromo- <i>N</i> <sup>2</sup> -(3-[[{(4 <i>R</i> )-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}phenyl]- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine
16	( <i>S</i> )-3-{3-[5-Bromo-4-(4-fluoro-phenylamino)-pyrimidin-2-ylamino]-phenoxy}-propane-1,2-diol
17	4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)- <i>N</i> -[1-(hydroxymethyl)-3-methylbutyl]benzamide
18	4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)- <i>N</i> -(5-isobutyl-4,5-dihydro-1,3-oxazol-2-yl)benzamide
19	<i>N</i> -(5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)- <i>N</i> -[4-(5-isobutyl-4,5-dihydro-1,3-oxazol-2-yl)phenyl]amine
20	ethyl 3-(4-[[2-({2-(diethylamino)ethoxy}-4'-methoxy-1,1'-biphenyl-4-yl)amino]-5-fluoro-4-pyrimidinyl]amino)phenoxy)benzoate
21	2-chloro- <i>N</i> -(2,4-dichloro-5-methoxyphenyl)-5-fluoro-4-pyrimidinamine and <i>N</i> -(2,4-dichloro-5-methoxyphenyl)- <i>N</i> -(2-[(2,4-dichloro-5-methoxyphenyl)amino]-5-fluoro-4-pyrimidinyl)amine

Example No.	IUPAC Name*
22	<i>N</i> -[4-({5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]acetamide
23	<i>N</i> -(4-amino-3-methylphenyl)- <i>N</i> -(5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)amine
24	<i>N</i> -(4-{5-fluoro-4-[5-(1-methylcyclopropyl)-2 <i>H</i> -pyrazol-3-ylamino]-pyrimidin-2-ylamino}-2-methylphenyl)-acetamide
25	<i>N</i> -[2-methyl-4-({5-methyl-4-[(2-methylbenzyl)amino]-2-pyrimidinyl}amino)phenyl]- <i>N</i> -(methylsulfonyl)methanesulfonamide
26	<i>N</i> -[4-({5-bromo-4-[(4-bromophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]-1-methyl-1 <i>H</i> -imidazole-4-sulfonamide
27	<i>N</i> -(5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)- <i>N</i> -(4-{4-[(4-fluorophenyl)sulfonyl]-1-piperazinyl}phenyl)amine
28	{5-bromo-4-[(4-methoxyphenyl)amino]pyrimidin-2-yl}{4-imidazolyl-3-methylphenyl}amine
29	<i>N</i> -[3-(1 <i>H</i> -pyrazol-3-yl)phenyl]- <i>N</i> -[2-[[3-(1 <i>H</i> -pyrazol-3-yl)phenyl]amino]-5-(trifluoromethyl)-4-pyrimidinyl]amine
30	2-[[2-[(6-oxo-6 <i>H</i> -benzo[c]chromen-2-yl)amino]-5-(trifluoromethyl)-4-pyrimidinyl]amino]-6 <i>H</i> -benzo[c]chromen-6-one hydrochloride
31	<i>N</i> <sup>2</sup> , <i>N</i> <sup>4</sup> -bis[4-(4-morpholinyl)phenyl]-5-(trifluoromethyl)-2,4-pyrimidinediamine trifluoroacetate
32	<i>N</i> -(5-bromo-4-[(4-fluorobenzyl)amino]-2-pyrimidinyl)- <i>N</i> -(3-(1 <i>H</i> -pyrazol-5-yl)phenyl)amine trifluoroacetate
33	5-bromo- <i>N</i> <sup>2</sup> -[4-(4-ethyl-1-piperazinyl)phenyl]- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine trifluoroacetate
34	<i>N</i> <sup>2</sup> -(1 <i>H</i> -1,2,3-benzotriazol-5-yl)-5-bromo- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine hydrochloride ( <i>N</i> <sup>2</sup> -(1 <i>H</i> -1,2,3-benzotriazol-5-yl)-5-bromo- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine trifluoroacetate)
35	<i>N</i> <sup>2</sup> -(1 <i>H</i> -1,2,3-benzotriazol-6-yl)-5-fluoro- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine trifluoroacetate

Example No.	IUPAC Name*
36	<i>N</i> -(5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)- <i>N</i> -(1-methyl-1 <i>H</i> -1,2,3-benzotriazol-6-yl)amine trifluoroacetate
37	5-bromo- <i>N</i> <sup>2</sup> -(2-ethyl-2 <i>H</i> -1,2,3-benzotriazol-5-yl)- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine trifluoroacetate
38	<i>N</i> -(5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)- <i>N</i> -(4-(1 <i>H</i> -pyrazol-3-yl)phenyl)amine
39	4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2-chlorobenzoic acid hydrochloride
40	4-[[4-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-5-bromo-2-pyrimidinyl]amino]benzoic acid
41	(3-[[4-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-5-bromo-2-pyrimidinyl]amino]phenyl)acetic acid dihydrochloride
42	4-[[4-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-5-bromo-2-pyrimidinyl]amino]-3-methoxybenzoic acid dihydrochloride
43	3-[[4-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-5-bromo-2-pyrimidinyl]amino]benzoic acid dihydrochloride
44	4-[[4-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-5-bromo-2-pyrimidinyl]amino]-3-methylbenzoic acid dihydrochloride
45	4-{2-[(5-bromo-2-[[4-(3-pyridinyloxy)phenyl]amino]-4-pyrimidinyl]amino]ethyl}benzenesulfonamide hydrochloride
46	(2 <i>R</i> )-3-[4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenoxy]-1,2-propanediol hydrochloride
47	3-[(5-bromo-4-[[4-(4-morpholinyl)phenyl]amino]-2-pyrimidinyl]amino]benzenesulfonamide trifluoroacetate
48	(4-[[4-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-5-bromo-2-pyrimidinyl]amino]phenyl)acetic acid hydrochloride
49	4-[[4-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-5-bromo-2-pyrimidinyl]amino]benzamide dihydrochloride
50	4-{2-[(5-bromo-2-[[3-(1 <i>H</i> -pyrazol-5-yl)phenyl]amino]-4-pyrimidinyl]amino]ethyl}benzenesulfonamide dihydrochloride

Example No.	IUPAC Name*
51	4-(2-([5-bromo-2-(2,3-dihydro-1,4-benzodioxin-6-ylamino)-4-pyrimidinyl]amino)ethyl)benzenesulfonamide
52	4-(2-([5-bromo-2-([4-(methylsulfonyl)phenyl]amino)-4-pyrimidinyl]amino)ethyl)benzenesulfonamide hydrochloride
53	4-(2-([5-bromo-2-(2,3-dihydro-1,4-benzodioxin-6-ylamino)-4-pyrimidinyl]amino)ethyl)benzenesulfonamide hydrochloride
54	<i>N</i> -(5-bromo-4-[(3-fluorophenyl)amino]-2-pyrimidinyl)- <i>N</i> -(3-(1-methyl-1 <i>H</i> -pyrazol-3-yl)phenyl)amine hydrochloride
55	<i>N</i> -(5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)- <i>N</i> -(4-(4-methyl-1-piperazinyl)phenyl)amine trifluoroacetate
56	<i>N</i> -(2,4-dichlorophenyl)- <i>N</i> -(2-([2-(diethylamino)ethoxy]-4'-methoxy-1,1'-biphenyl-4-yl]amino)-5-fluoro-4-pyrimidinyl]amine
57	3-[3-([5-bromo-2-([4-fluorophenyl)amino]-4-pyrimidinyl]amino)phenoxy]-1,2-propanediol hydrochloride
58	<i>N</i> -(2,4-dichloro-5-methoxyphenyl)- <i>N</i> -(2-([2-(diethylamino)ethoxy]-4'-methoxy-1,1'-biphenyl-4-yl]amino)-5-fluoro-4-pyrimidinyl]amine
59	<i>N</i> -(2,4-dichloro-5-methoxyphenyl)- <i>N</i> -(2-([3-(2-(diethylamino)ethoxy)-4-(1 <i>H</i> -indol-5-yl)phenyl]amino)-5-fluoro-4-pyrimidinyl]amine
60	<i>N</i> <sup>2</sup> -(1 <i>H</i> -1,2,3-benzotriazol-5-yl)- <i>N</i> <sup>1</sup> -(1 <i>H</i> -1,2,3-benzotriazol-6-yl)-5-bromo-2,4-pyrimidinediamine trifluoroacetate
61	5-chloro-4-([4-fluorophenyl]amino)- <i>N</i> -(3-(1 <i>H</i> -pyrazol-5-yl)phenyl)-2-pyrimidinaminium trifluoroacetate
62	<i>N</i> -(5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)- <i>N</i> -(2-methyl-2 <i>H</i> -indazol-5-yl)amine
63	<i>N</i> -(5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)- <i>N</i> -(2-methyl-2 <i>H</i> -indazol-6-yl)amine
64	4-([5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl]amino)-2-methoxybenzoic acid compound with trifluoroacetic acid (1:1)

Example No.	IUPAC Name*
65	<i>N</i> <sup>4</sup> -(1 <i>H</i> -1,2,3-benzotriazol-6-yl)-5-bromo- <i>N</i> <sup>2</sup> -[4-(trifluoromethyl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
66	<i>N</i> <sup>4</sup> -(1 <i>H</i> -1,2,3-benzotriazol-6-yl)-5-bromo- <i>N</i> <sup>2</sup> -[3-(1 <i>H</i> -pyrazol-4-yl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
67	<i>N</i> <sup>4</sup> -(1 <i>H</i> -1,2,3-benzotriazol-6-yl)-5-bromo- <i>N</i> <sup>2</sup> -[4-(4-morpholinyl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
68	4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)- <i>N</i> -methoxybenzamide
69	4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)- <i>N</i> -hydroxybenzamide
70	(1 <i>E</i> )-1-[4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenyl]ethanone <i>O</i> -methyloxime
71	trifluoroacetic acid compound with <i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[3-(3-isoxazolyl)phenyl]amine (1:1)
72	trifluoroacetic acid compound with <i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[3-(5-isoxazolyl)phenyl]amine (1:1)
73	<i>N</i> -{5-bromo-4-[(3-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[3-(3-isoxazolyl)phenyl]amine trifluoroacetate
74	trifluoroacetic acid compound with <i>N</i> -{5-bromo-4-[(3-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[3-(5-isoxazolyl)phenyl]amine (1:1)
75	4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenol hydrochloride
76	3-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenol hydrochloride
77	(1 <i>E</i> )-5-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2,3-dihydro-1 <i>H</i> -inden-1-one oxime trifluoroacetate
78	(1 <i>E</i> )-5-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2,3-dihydro-1 <i>H</i> -inden-1-one <i>O</i> -methyloxime trifluoroacetate

Example No.	IUPAC Name*
79	1-({4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenyl}sulfanyl)-3-(diethylamino)-2-propanol hydrochloride
80	4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2-methoxybenzoic acid
81	4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)- <i>N</i> -(tetrahydro-2 <i>H</i> -pyran-2-yloxy)benzamide
82	5-fluoro- <i>N</i> <sup>2</sup> -[3-fluoro-4-(4-morpholinyl)phenyl]- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine trifluoroacetate
83	5-chloro- <i>N</i> <sup>2</sup> -[3-fluoro-4-(4-morpholinyl)phenyl]- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine trifluoroacetate
84	5-bromo- <i>N</i> <sup>2</sup> -[3-fluoro-4-(4-morpholinyl)phenyl]- <i>N</i> <sup>4</sup> -[4-(4-morpholinyl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
85	4-({5-bromo-2-[[3-fluoro-4-(4-morpholinyl)phenyl]amino]-4-pyrimidinyl}amino)benzenesulfonamide trifluoroacetate
86	<i>N</i> <sup>2</sup> -(1 <i>H</i> -1,2,3-benzotriazol-5-yl)-5-chloro- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine trifluoroacetate
87	5-bromo- <i>N</i> <sup>2</sup> -{2-[2-(diethylamino)ethoxy]-3'-methoxy-1,1'-biphenyl-4-yl}- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine
88	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -{3-[2-(1 <i>H</i> -imidazol-1-yl)ethoxy]-4-methoxyphenyl}amine
89	5-bromo- <i>N</i> <sup>2</sup> -{3-[2-(diethylamino)ethoxy]-4-methoxyphenyl}- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine
90	4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)- <i>N</i> -hydroxybenzamide trifluoroacetate
91	4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)- <i>N</i> -methoxybenzamide trifluoroacetate
92	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -{4-methoxy-3-[2-(1-pyrrolidinyl)ethoxy]phenyl}amine
93	5-bromo- <i>N</i> <sup>2</sup> -[3-[2-(diethylamino)ethoxy]-4-(8-quinolinyl)phenyl]- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine

Example No.	IUPAC Name*
94	{4'-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2'-[2-(diethylamino)ethoxy]-1,1'-biphenyl-4-yl}acetonitrile
95	4'-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2'-[2-(diethylamino)ethoxy]-1,1'-biphenyl-3-carbonitrile
96	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -{4-(1 <i>H</i> -indol-5-yl)-3-[2-(1-pyrrolidinyl)ethoxy]phenyl}amine
97	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -{4-methoxy-3-[2-(4-morpholinyl)ethoxy]phenyl}amine
98	5-bromo- <i>N</i> <sup>2</sup> -(1-ethyl-1 <i>H</i> -indazol-5-yl)- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine
99	<i>N</i> <sup>4</sup> -(1 <i>H</i> -1,2,3-benzotriazol-6-yl)-5-bromo- <i>N</i> <sup>2</sup> -(3,5-dimethoxyphenyl)-2,4-pyrimidinediamine hydrochloride
100	<i>N</i> <sup>4</sup> -(1 <i>H</i> -1,2,3-benzotriazol-6-yl)-5-bromo- <i>N</i> <sup>2</sup> -[4-(4-morpholinyl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
101	5-bromo- <i>N</i> <sup>2</sup> -{2-[2-(diethylamino)ethoxy]-3'-methoxy-1,1'-biphenyl-4-yl}- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine
102	5-bromo- <i>N</i> <sup>2</sup> -{2-[2-(diethylamino)ethoxy]-4'-methoxy-1,1'-biphenyl-4-yl}- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine
103	5-bromo- <i>N</i> <sup>2</sup> -{1-[2-(diethylamino)ethyl]-1 <i>H</i> -indol-5-yl}- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine
104	5-bromo- <i>N</i> <sup>2</sup> -(1-ethyl-1 <i>H</i> -indazol-5-yl)- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine
105	(2 <i>R</i> )-3-[3-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenoxy]-1,2-propanediol
106	(2 <i>S</i> )-3-[5-({5-bromo-4-[(4-methoxyphenyl)amino]-2-pyrimidinyl}amino)-1 <i>H</i> -indol-1-yl]-1,2-propanediol
107	5-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-1 <i>H</i> -indole-3-carboxamide trifluoroacetate
108	<i>N</i> -(4-amino-3-methylphenyl)- <i>N</i> -(4-[(4-chlorophenyl)amino]-5-fluoro-2-pyrimidinyl)amine

Example No.	IUPAC Name*
109	<i>N</i> -(4-amino-3-methylphenyl)- <i>N</i> -{4-[(4-bromophenyl)amino]-5-fluoro-2-pyrimidinyl}amine
110	<i>N</i> -(4-amino-3-methylphenyl)- <i>N</i> -{4-[(2,4-dichlorobenzyl)amino]-5-fluoro-2-pyrimidinyl}amine
111	<i>N</i> -[5-bromo-2-({4'-(dimethylamino)-2-[2-(1-pyrrolidinyl)ethoxy]-1,1'-biphenyl-4-yl}amino)-4-pyrimidinyl]- <i>N</i> -(4-fluorophenyl)amine
113	<i>N</i> <sup>2</sup> -(1 <i>H</i> -benzimidazol-5-yl)- <i>N</i> <sup>4</sup> -(1 <i>H</i> -1,2,3-benzotriazol-6-yl)-5-bromo-2,4-pyrimidinediamine trifluoroacetate
114	5-bromo- <i>N</i> <sup>4</sup> -(1-methyl-1 <i>H</i> -1,2,3-benzotriazol-5-yl)- <i>N</i> <sup>2</sup> -[4-(4-morpholinyl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
115	5-bromo- <i>N</i> <sup>4</sup> -(1-methyl-1 <i>H</i> -1,2,3-benzotriazol-6-yl)- <i>N</i> <sup>2</sup> -[4-(4-morpholinyl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
116	5-chloro- <i>N</i> <sup>4</sup> -(4-fluorophenyl)- <i>N</i> <sup>2</sup> -[4-(1 <i>H</i> -pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
117	<i>N</i> <sup>4</sup> -(1 <i>H</i> -1,2,3-benzotriazol-5-yl)-5-bromo- <i>N</i> <sup>2</sup> -(1 <i>H</i> -indol-5-yl)-2,4-pyrimidinediamine trifluoroacetate
118	5-bromo- <i>N</i> <sup>2</sup> -[2-[2-(diethylamino)ethoxy]-4'-(trifluoromethyl)-1,1'-biphenyl-4-yl]- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine
119	<i>N</i> -[4-({5-fluoro-4-[(3-fluorophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]acetamide
120	<i>N</i> -[4-({5-fluoro-4-[(4-methylphenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]acetamide
121	<i>N</i> -[4-({5-fluoro-4-[(4-methylphenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]acetamide
122	(1) <i>N</i> -(4-aminophenyl)- <i>N</i> -{5-bromo-4-[(2-methylbenzyl)amino]-2-pyrimidinyl}amine
123	<i>N</i> -[4-({5-bromo-4-[(4-bromophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]- <i>N,N</i> -dimethylsulfamide

Example No.	IUPAC Name*
124	<i>N</i> -[2-chloro-4-({5-fluoro-4-[(3-methoxyphenyl)amino]-2-pyrimidinyl}amino)phenyl]acetamide
125	<i>N</i> -[4-({5-bromo-4-[(4-bromophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]acetamide
126	<i>N</i> -[4-({5-bromo-4-[(4-chlorophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]acetamide
127	<i>N</i> -[4-({5-bromo-4-[(4-chlorophenyl)amino]-2-pyrimidinyl}amino)-2-chlorophenyl]acetamide
128	<i>N</i> -{5-fluoro-4-[(4-methylphenyl)amino]-2-pyrimidinyl}- <i>N</i> -[4-(4-methyl-1-piperazinyl)phenyl]amine
129	<i>N</i> -(4-bromophenyl)- <i>N</i> -(5-fluoro-2-{[4-(4-methyl-1-piperazinyl)phenyl]amino}-4-pyrimidinyl)amine
130	<i>N</i> -(4-amino-3-methylphenyl)- <i>N</i> -{5-fluoro-4-[(4-methylphenyl)amino]-2-pyrimidinyl}amine
131	<i>N</i> -(4-amino-3-methylphenyl)- <i>N</i> -{5-fluoro-4-[(3-fluorophenyl)amino]-2-pyrimidinyl}amine
132	<i>N</i> -[5-fluoro-2-(1 <i>H</i> -indol-5-ylamino)-4-pyrimidinyl]- <i>N</i> -(3-methoxyphenyl)amine
133	5-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2-(1 <i>H</i> -pyrazol-3-yl)phenol
134	<i>N</i> -(4-chlorophenyl)- <i>N</i> -(5-fluoro-2-{[4-(1-piperidinyl)phenyl]amino}-4-pyrimidinyl)amine
135	4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)- <i>N</i> -(2-hydroxyethyl)benzamide 4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)- <i>N</i> -(2-hydroxyethyl)benzamide
136	4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)- <i>N</i> -(cyanoacetyl)benzohydrazide
137	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[3-(1 <i>H</i> -imidazol-1-yl methyl)phenyl]amine
138	<i>N</i> -{5-bromo-4-[(3-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[3-(1-methyl-1 <i>H</i> -pyrazol-5-yl)phenyl]amine hydrochloride
139	<i>N</i> -(1 <i>H</i> -indol-5-yl)- <i>N</i> -{5-methyl-4-[(2-methylbenzyl)amino]-2-pyrimidinyl}amine

Example No.	IUPAC Name*
140	<i>N</i> -{5-bromo-4-[(2,5-dichlorobenzyl)amino]-2-pyrimidinyl}- <i>N</i> -(1 <i>H</i> -indol-5-yl)amine
141	<i>N</i> -[4-({5-bromo-4-[(4-chlorophenyl)amino]-2-pyrimidinyl}amino)phenyl]acetamide
142	<i>N</i> -[4-({5-chloro-4-[(2-methylbenzyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]- <i>N</i> -(methylsulfonyl)methanesulfonamide
143	<i>N</i> -[2-methyl-4-({5-methyl-4-[(2-methylbenzyl)amino]-2-pyrimidinyl}amino)phenyl]methanesulfonamide
144	<i>N</i> -(2-methylbenzyl)- <i>N</i> -(5-methyl-2-[[4-(4-methyl-1-piperazinyl)phenyl]amino]-4-pyrimidinyl)amine
145	<i>N</i> -(2-methylbenzyl)- <i>N</i> -(5-methyl-2-[(1-methyl-1 <i>H</i> -indol-5-yl)amino]-4-pyrimidinyl)amine
146	<i>N</i> -[4-(1 <i>H</i> -imidazol-1-yl)phenyl]- <i>N</i> -(5-methyl-4-[(2-methylbenzyl)amino]-2-pyrimidinyl)amine
147	<i>N</i> -(4-amino-3-methylphenyl)- <i>N</i> -[4-[(3-chlorophenyl)amino]-5-fluoro-2-pyrimidinyl]amine
148	4-({5-bromo-4-[(4-methoxyphenyl)amino]-2-pyrimidinyl}amino)- <i>N</i> -methylbenzamide
149	(1 <i>E</i> )-6-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-3,4-dihydro-1(2 <i>H</i> )-naphthalenone <i>O</i> -methyloxime
150	5'-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2'-(4-methyl-1-piperazinyl)-1,1'-biphenyl-4-carbonitrile
151	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -(1-methyl-1 <i>H</i> -indol-5-yl)amine
152	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -(1-propyl-1 <i>H</i> -indol-5-yl)amine
153	4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)- <i>N</i> -(2,3-dihydroxypropyl)benzamide
154	<i>N</i> -(5-bromo-2-[[4-(1 <i>H</i> -imidazol-1-yl)phenyl]amino]-4-pyrimidinyl)- <i>N</i> -(4-methoxyphenyl)amine

Example No.	IUPAC Name*
155	5-bromo- <i>N</i> <sup>1</sup> -(4-fluorophenyl)- <i>N</i> <sup>2</sup> -(4-(4-methyl-1-piperazinyl)-3-[[2-(4-morpholinyl)ethyl]amino]phenyl)-2,4-pyrimidinediamine
156	<i>N</i> -{5-bromo-4-[(4-bromophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[4-(4-methyl-1-piperazinyl)phenyl]amine
157	<i>N</i> -[4-({5-bromo-4-[(2-chlorobenzyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]- <i>N</i> -(methylsulfonyl)methanesulfonamide
158	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[3-(1-methyl-1 <i>H</i> -pyrazol-5-yl)phenyl]amine
159	5-bromo- <i>N</i> <sup>4</sup> -(4-methoxyphenyl)- <i>N</i> <sup>2</sup> -[3-(1-methyl-1 <i>H</i> -pyrazol-5-yl)phenyl]-2,4-pyrimidinediamine
160	5-({5-bromo-4-[(4-methoxyphenyl)amino]-2-pyrimidinyl}amino)-2-(1 <i>H</i> -pyrazol-3-yl)phenol
161	5-bromo- <i>N</i> <sup>2</sup> -[4-(4-ethyl-1 <i>H</i> -pyrazol-3-yl)phenyl]- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine
162	5-bromo- <i>N</i> <sup>2</sup> -[4-(4-ethyl-1 <i>H</i> -pyrazol-3-yl)phenyl]- <i>N</i> <sup>4</sup> -(3-fluorophenyl)-2,4-pyrimidinediamine
163	3-[[5-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2-methoxybenzyl]amino]-1,2-propanediol
164	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -(4-methoxy-3-[[2-(4-morpholinyl)ethoxy]methyl]phenyl)amine
165	(2 <i>R</i> )-3-[5-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-1 <i>H</i> -indol-1-yl]-1,2-propanediol
166	<i>N</i> -[4-({5-bromo-4-[(4-bromophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]- <i>N</i> -(methylsulfonyl)methanesulfonamide
167	<i>N</i> -[4-({4-[(3-chlorophenyl)amino]-5-fluoro-2-pyrimidinyl}amino)-2-methylphenyl]methanesulfonamide
168	<i>N</i> -[4-({5-fluoro-4-[(4-methylphenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]methanesulfonamide
169	(2 <i>R</i> )-3-[5-({5-bromo-4-[(4-methoxyphenyl)amino]-2-pyrimidinyl}amino)-1 <i>H</i> -indol-1-yl]-1,2-propanediol

Example No.	IUPAC Name*
170	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[4-(1-pyrrolidinylmethyl)phenyl]amine
171	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[3-(1-pyrrolidinylmethyl)phenyl]amine
172	<i>N</i> -[5-bromo-2-({4'-(dimethylamino)-2-[2-(1 <i>H</i> -imidazol-1-yl)ethoxy]-1,1'-biphenyl-4-yl}amino)-4-pyrimidinyl]- <i>N</i> -(4-fluorophenyl)amine
173	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]amine
174	5-bromo- <i>N</i> <sup>2</sup> -(4,5-dihydro-2 <i>H</i> -benzo[g]indazol-7-yl)- <i>N</i> <sup>4</sup> -(4-fluorophenyl)-2,4-pyrimidinediamine
175	5-bromo- <i>N</i> <sup>2</sup> -(4,5-dihydro-2 <i>H</i> -benzo[g]indazol-7-yl)- <i>N</i> <sup>4</sup> -(3-fluorophenyl)-2,4-pyrimidinediamine
176	5-bromo- <i>N</i> <sup>2</sup> -(4,5-dihydro-2 <i>H</i> -benzo[g]indazol-7-yl)- <i>N</i> <sup>4</sup> -(4-methoxyphenyl)-2,4-pyrimidinediamine
177	<i>N</i> -[4-({5-bromo-4-[(4-chlorophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]- <i>N</i> -(methylsulfonyl)methanesulfonamide
178	<i>N</i> -[4-({5-bromo-4-[(4-(4-morpholinyl)phenyl]amino)-2-pyrimidinyl}amino)-2-methylphenyl]- <i>N</i> -(methylsulfonyl)methanesulfonamide
179	<i>N</i> -(4-amino-3-methylphenyl)- <i>N</i> -{5-bromo-4-[(4-chlorophenyl)amino]-2-pyrimidinyl}amine
180	<i>N</i> -[4-({5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]methanesulfonamide
181	<i>N</i> -[4-({5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]- <i>N</i> -(methylsulfonyl)methanesulfonamide
182	<i>N</i> -[4-({5-bromo-4-[(2-chlorobenzyl)amino]-2-pyrimidinyl}amino)-2-chlorophenyl]- <i>N</i> -(methylsulfonyl)methanesulfonamide
183	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[4-(1 <i>H</i> -imidazol-1-ylmethyl)phenyl]amine

Example No.	IUPAC Name*
184	<i>N</i> -[4-({5-fluoro-4-[(4-methylphenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]methanesulfonamide
185	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[3-methoxy-4-(4-pyridinyl)phenyl]amine
186	<i>N</i> -[4-({5-bromo-4-[(4-chlorophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]-1-methyl-1 <i>H</i> -imidazole-4-sulfonamide
187	<i>N</i> -[4-({5-bromo-4-[(4-chlorophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]-1-methyl-1 <i>H</i> -imidazole-4-sulfonamide
188	<i>N</i> -[4-({5-bromo-4-[(4-chlorophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]- <i>N</i> -(methylsulfonyl)methanesulfonamide
189	<i>N</i> -[4-({5-bromo-4-[(4-chlorophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]methanesulfonamide
190	<i>N</i> -[3-(1,3-benzodioxol-5-yl)-4-(4-methyl-1-piperazinyl)phenyl]- <i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amine
191	<i>N</i> -[4-({4-[(2,4-dichlorophenyl)amino]-5-fluoro-2-pyrimidinyl}amino)-2-methylphenyl]- <i>N</i> -(methylsulfonyl)methanesulfonamide
192	<i>N</i> -[5-({4-({5-chloro-4-[(2-methylbenzyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl}amino)sulfonyl)-4-methyl-1,3-thiazol-2-yl]acetamide
193	<i>N</i> -[4-(4-acetyl-1-piperazinyl)phenyl]- <i>N</i> -{5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amine
194	<i>N</i> -(2-chlorobenzyl)- <i>N</i> -(5-methyl-2-[[4-(1-piperazinyl)phenyl]amino]-4-pyrimidinyl)amine
195	(2 <i>R</i> )-3-{5-[(5-bromo-2-[[4-(1 <i>H</i> -pyrazol-3-yl)phenyl]amino]-4-pyrimidinyl}amino]-1 <i>H</i> -indol-1-yl}-1,2-propanediol
196	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[3-(4-morpholinylmethyl)phenyl]amine
197	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[3-(1 <i>H</i> -imidazol-1-ylmethyl)-4-methoxyphenyl]amine

Example No.	IUPAC Name*
198	<i>N</i> -{5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[4-(1-piperazinyl)phenyl]amine
199	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -[4-methoxy-3-(4-morpholinylmethyl)phenyl]amine
200	<i>N</i> -{5-bromo-4-[(3-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -{3-[2-(1 <i>H</i> -imidazol-1-yl)ethoxy]-4-methoxyphenyl}amine
201	<i>N</i> -[5-bromo-2-({3-[2-(1 <i>H</i> -imidazol-1-yl)ethoxy]-4-methoxyphenyl}amino)-4-pyrimidinyl]- <i>N</i> -(4-methoxyphenyl)amine
202	<i>N</i> -{5-bromo-4-[(1-methyl-1 <i>H</i> -indol-5-yl)amino]-2-pyrimidinyl}- <i>N</i> -[4-(1 <i>H</i> -pyrazol-3-yl)phenyl]amine
203	5-bromo- <i>N</i> <sup>2</sup> -(4,5-dihydro-2 <i>H</i> -benzo[ <i>g</i> ]indazol-7-yl)- <i>N</i> <sup>4</sup> -(1-methyl-1 <i>H</i> -indol-5-yl)-2,4-pyrimidinediamine
204	5-({5-bromo-4-[(4-methoxyphenyl)amino]-2-pyrimidinyl}amino)-1,3-dihydro-2 <i>H</i> -benzimidazol-2-one
205	<i>N</i> -acetyl-4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)benzohydrazide
206	<i>N</i> -[(3 <i>aS</i> )-2,3,3 <i>a</i> ,4-tetrahydro-1 <i>H</i> -pyrrolo[2,1- <i>c</i> ][1,4]benzoxazin-7-yl]- <i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amine
207	4-[(5-bromo-2-({3-fluoro-4-(4-morpholinyl)phenyl}amino)-4-pyrimidinyl)amino]benzenesulfonamide trifluoroacetate
208	<i>N</i> -(2-chlorobenzyl)- <i>N</i> -[5-methyl-2-({4-[4-(methylsulfonyl)-1-piperazinyl]phenyl}amino)-4-pyrimidinyl]amine
209	<i>N</i> -(2-chlorobenzyl)- <i>N</i> -(5-methyl-2-[[4-(1,2,3-thiadiazol-4-yl)phenyl]amino]-4-pyrimidinyl)amine
210	5-bromo- <i>N</i> <sup>4</sup> -[3-(1 <i>H</i> -pyrazol-3-yl)phenyl]- <i>N</i> <sup>2</sup> -[4-(1 <i>H</i> -pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
211	<i>N</i> <sup>2</sup> -(1 <i>H</i> -1,2,3-benzotriazol-5-yl)-5-bromo- <i>N</i> <sup>4</sup> -[3-(1 <i>H</i> -pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
212	5-bromo- <i>N</i> <sup>2</sup> -(1 <i>H</i> -indazol-5-yl)- <i>N</i> <sup>4</sup> -[3-(1 <i>H</i> -pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine trifluoroacetate

Example No.	IUPAC Name*
213	5-[(5-bromo-4-[[3-(1 <i>H</i> -pyrazol-3-yl)phenyl]amino]-2-pyrimidinyl)amino]-1 <i>H</i> -benzimidazole-2-thiol trifluoroacetate
214	<i>N</i> -[2-methyl-4-({5-methyl-4-[(2-methylbenzyl)amino]-2-pyrimidinyl)amino}phenyl]acetamide
215	<i>N</i> -(4-amino-3-methylphenyl)- <i>N</i> -(5-methyl-4-[(2-methylbenzyl)amino]-2-pyrimidinyl)amine
216	1-[4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)amino]-2-fluorophenyl]-3-piperidinecarboxylic acid trifluoroacetate
217	methyl 4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)amino)-2-(2-hydroxyethoxy)benzoate
218	4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)amino)-2-(2-hydroxyethoxy)benzoic acid
219	5-bromo- <i>N</i> 2-(4-methoxy-3-[2-(4-morpholinyl)ethoxy]phenyl)- <i>N</i> 4-(4-methoxyphenyl)-2,4-pyrimidinediamine trifluoroacetate
220	4-[(5-fluoro-4-[[3-(1 <i>H</i> -pyrazol-3-yl)phenyl]amino]-2-pyrimidinyl)amino]phenol trifluoroacetate
221	3-[(5-fluoro-4-[[3-(1 <i>H</i> -pyrazol-3-yl)phenyl]amino]-2-pyrimidinyl)amino]phenol trifluoroacetate
222	5-[(5-fluoro-4-[[3-(1 <i>H</i> -pyrazol-3-yl)phenyl]amino]-2-pyrimidinyl)amino]-2-methoxyphenol trifluoroacetate
223	5-fluoro- <i>N</i> <sup>2</sup> -(1 <i>H</i> -indazol-5-yl)- <i>N</i> <sup>4</sup> -(3-(1 <i>H</i> -pyrazol-3-yl)phenyl)-2,4-pyrimidinediamine trifluoroacetate
224	<i>N</i> -[5-bromo-2-(1 <i>H</i> -indazol-5-ylamino)-4-pyrimidinyl]- <i>N</i> -(1 <i>H</i> -indol-5-yl)amine
225	<i>N</i> -(1 <i>H</i> -1,2,3-benzotriazol-5-yl)- <i>N</i> -[5-bromo-4-(1 <i>H</i> -indol-4-ylamino)-2-pyrimidinyl]amine
226	<i>N</i> -[5-bromo-2-(1 <i>H</i> -indazol-5-ylamino)-4-pyrimidinyl]- <i>N</i> -(1 <i>H</i> -indol-4-yl)amine
227	<i>N</i> -(4-amino-3-methylphenyl)- <i>N</i> -(5-bromo-4-[(4-methoxyphenyl)amino]-2-pyrimidinyl)amine

Example No.	IUPAC Name*
228	<i>N</i> -{5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}- <i>N</i> -{3-methoxy-4-[2-(4-morpholinyl)ethoxy]phenyl}amine
229	{5-chloro-4-[(4-fluorophenyl)amino]pyrimidin-2-yl}{4-imidazolyl-3-methylphenyl}amine
230	(4-imidazolyl-3-methylphenyl)[5-methyl-4-({2-(trifluoromethyl)phenyl}methyl)amino]pyrimidin-2-yl}amine
231	(4-{[5-chloro-4-({2-(trifluoromethyl)phenyl}methyl)amino]pyrimidin-2-yl}amino)-2-(trifluoromethyl)phenyl){(1-methylimidazol-4-yl)sulfonyl}amine
232	{[(1-methylimidazol-4-yl)sulfonyl](2-methyl-4-{{5-methyl-4-({2-(trifluoromethyl)phenyl}methyl)amino}pyrimidin-2-yl}amino)phenyl}amine
233	4-({5-bromo-4-[(3-ethynylphenyl)amino]-2-pyrimidinyl}amino)phenol trifluoroacetate
234	5-({5-bromo-4-[(3-ethynylphenyl)amino]-2-pyrimidinyl}amino)-2-methoxyphenol trifluoroacetate
235	5-bromo- <i>N</i> <sup>2</sup> -(3,4-dimethoxyphenyl)- <i>N</i> <sup>4</sup> -(3-ethynylphenyl)-2,4-pyrimidinediamine trifluoroacetate
236	5-bromo- <i>N</i> <sup>4</sup> -(3-ethynylphenyl)- <i>N</i> <sup>2</sup> -[4-(4-morpholinyl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
237	<i>N</i> <sup>2</sup> -(1 <i>H</i> -1,2,3-benzotriazol-5-yl)-5-bromo- <i>N</i> <sup>4</sup> -(3-ethynylphenyl)-2,4-pyrimidinediamine
238	5-bromo- <i>N</i> <sup>4</sup> -(3-ethynylphenyl)- <i>N</i> <sup>2</sup> -(1 <i>H</i> -indazol-5-yl)-2,4-pyrimidinediamine trifluoroacetate
239	5-({5-bromo-4-[(3-ethynylphenyl)amino]-2-pyrimidinyl}amino)-1 <i>H</i> -benzimidazol-2-ylhydrosulfide trifluoroacetate
240	5-bromo- <i>N</i> <sup>2</sup> -[4-(4-morpholinyl)phenyl]- <i>N</i> <sup>4</sup> -[4-(trifluoromethyl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
241	5-({5-bromo-4-[(4-methoxyphenyl)amino]pyrimidin-2-yl}amino)indolin-2-one

Example No.	IUPAC Name*
242	1-[4-({5-bromo-2-[(3-hydroxy-4-methoxyphenyl)amino]-4-pyrimidinyl}amino)phenyl]ethanone trifluoroacetate
243	1-[4-({5-bromo-2-[[4-(1 <i>H</i> -pyrazol-3-yl)phenyl]amino]-4-pyrimidinyl}amino)phenyl]ethanone trifluoroacetate
244	1-[4-({2-(1 <i>H</i> -1,2,3-benzotriazol-5-ylamino)-5-bromo-4-pyrimidinyl}amino)phenyl]ethanone trifluoroacetate
245	1-[4-({5-bromo-2-(1 <i>H</i> -indazol-5-ylamino)-4-pyrimidinyl}amino)phenyl]ethanone trifluoroacetate
246	1-[4-({5-bromo-2-[(2-sulfanyl-1 <i>H</i> -benzimidazol-5-yl)amino]-4-pyrimidinyl}amino)phenyl]ethanone trifluoroacetate
247	<i>N</i> <sup>2</sup> -(1 <i>H</i> -1,2,3-benzotriazol-5-yl)-5-bromo- <i>N</i> <sup>4</sup> -[4-(trifluoromethyl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
248	<i>N</i> -(1 <i>H</i> -1,2,3-benzotriazol-5-yl)- <i>N</i> -[5-bromo-4-(2,3-dihydro-1 <i>H</i> -inden-5-ylamino)-2-pyrimidinyl]amine
249	<i>N</i> -[5-bromo-4-(2,3-dihydro-1 <i>H</i> -inden-5-ylamino)-2-pyrimidinyl]- <i>N</i> -(1 <i>H</i> -indazol-5-yl)amine
250	5-bromo- <i>N</i> <sup>2</sup> -[4-(4-methyl-1-piperazinyl)phenyl]- <i>N</i> <sup>4</sup> -[4-(1 <i>H</i> -pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
251	4-[(5-bromo-4-[[4-(1 <i>H</i> -pyrazol-3-yl)phenyl]amino]-2-pyrimidinyl)amino]phenol trifluoroacetate
252	3-[(5-bromo-4-[[4-(1 <i>H</i> -pyrazol-3-yl)phenyl]amino]-2-pyrimidinyl)amino]phenol trifluoroacetate
253	5-[(5-bromo-4-[[4-(1 <i>H</i> -pyrazol-3-yl)phenyl]amino]-2-pyrimidinyl)amino]-2-methoxyphenol trifluoroacetate
254	5-bromo- <i>N</i> <sup>2</sup> -(3,4-dimethoxyphenyl)- <i>N</i> <sup>4</sup> -[4-(1 <i>H</i> -pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
255	5-bromo- <i>N</i> <sup>2</sup> , <i>N</i> <sup>4</sup> -bis[4-(1 <i>H</i> -pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
256	5-bromo- <i>N</i> <sup>2</sup> -[4-methoxy-3-[2-(4-morpholinyl)ethoxy]phenyl]- <i>N</i> <sup>4</sup> -[3-(1 <i>H</i> -pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine trifluoroacetate

Example No.	IUPAC Name*
257	5-bromo- <i>N</i> <sup>1</sup> -(3-ethynylphenyl)- <i>N</i> <sup>2</sup> -(4-methoxy-3-[2-(4-morpholinyl)ethoxy]phenyl)-2,4-pyrimidinediamine trifluoroacetate
258	5-bromo- <i>N</i> <sup>1</sup> -(1 <i>H</i> -indol-5-yl)- <i>N</i> <sup>2</sup> -(4-methoxy-3-[2-(4-morpholinyl)ethoxy]phenyl)-2,4-pyrimidinediamine trifluoroacetate
259	5-bromo- <i>N</i> <sup>2</sup> -(4-methoxy-3-[2-(4-morpholinyl)ethoxy]phenyl)- <i>N</i> <sup>1</sup> -[3-(1 <i>H</i> -pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
260	1-(3-[[5-bromo-2-({4-methoxy-3-[2-(4-morpholinyl)ethoxy]phenyl)amino]-4-pyrimidinyl]amino]phenyl)ethanone trifluoroacetate
261	1-(4-[[5-bromo-2-({4-methoxy-3-[2-(4-morpholinyl)ethoxy]phenyl)amino]-4-pyrimidinyl]amino]phenyl)-1-butanone trifluoroacetate
262	5-bromo- <i>N</i> <sup>2</sup> -[4-(4-methyl-1-piperazinyl)phenyl]- <i>N</i> <sup>1</sup> -[3-(1 <i>H</i> -pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
263	5-bromo- <i>N</i> <sup>1</sup> -(3-ethynylphenyl)- <i>N</i> <sup>2</sup> -[4-(4-methyl-1-piperazinyl)phenyl]-2,4-pyrimidinediamine trifluoroacetate
264	1-(4-[[5-bromo-2-[[4-(4-methyl-1-piperazinyl)phenyl]amino]-4-pyrimidinyl]amino]phenyl)ethanone trifluoroacetate+C11
265	1-(3-[[5-bromo-2-[[4-(4-methyl-1-piperazinyl)phenyl]amino]-4-pyrimidinyl]amino]phenyl)ethanone trifluoroacetate
266	1-(4-[[5-bromo-2-[[4-(4-methyl-1-piperazinyl)phenyl]amino]-4-pyrimidinyl]amino]phenyl)-1-butanone trifluoroacetate
267	<i>N</i> -(5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)- <i>N</i> -[3-(1 <i>H</i> -pyrazol-3-yl)phenyl]amine trifluoroacetate
268	5-[(5-fluoro-4-[[3-(1 <i>H</i> -pyrazol-3-yl)phenyl]amino]-2-pyrimidinyl)amino]-1 <i>H</i> -benzimidazole-2-thiol trifluoroacetate

Example No.	IUPAC Name*
112	4-[[4-(1 <i>H</i> -1,2,3-benzotriazol-6-ylamino)-5-bromo-2-pyrimidinyl]amino}benzenecarboximidamide trifluoroacetate

\*The IUPAC Names were obtained using the ACD/ILab Web service.

The compounds of this invention may contain one or more asymmetric centers, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (*R*) or (*S*) configuration or (*R,S*) configuration. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds. Substituents on a ring may also be present in either *cis* or *trans* form, and a substituent on a double bond may be present in either *Z* or *E* form. It is intended that all such configurations (including enantiomers and diastereomers) are included within the scope of the present invention. Preferred compounds are those with the absolute configuration of the compound of this invention which produces the more desirable biological activity. Separated, pure or partially purified isomers or racemic mixtures of the compounds of this invention are also included within the scope of the present invention.

The use of pharmaceutically acceptable salts of the compounds of Formula I are also within the scope of this invention. The term "pharmaceutically acceptable salt" refers to either inorganic or organic acid or base salts of a compound of the present invention that have properties acceptable for the therapeutic use intended. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," *J. Pharm. Sci.* 1977, 66, 1-19.

Representative salts of the compounds of this invention include the conventional non-toxic salts and the quaternary ammonium salts that are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, tartrate, thiocyanate, tosylate, and undecanoate. The term acid addition salts also comprises the hydrates and the solvent addition forms which the compounds of this invention are able to form. Examples of such forms are, for example,

hydrates, alcoholates and the like.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, and dibutyl sulfate; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides including benzyl and phenethyl bromides, and others.

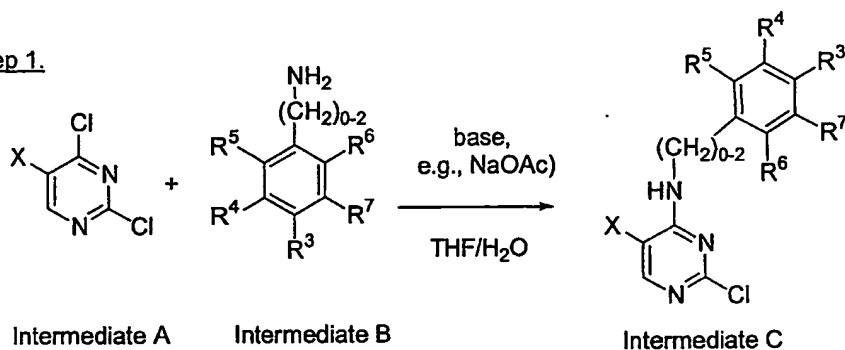
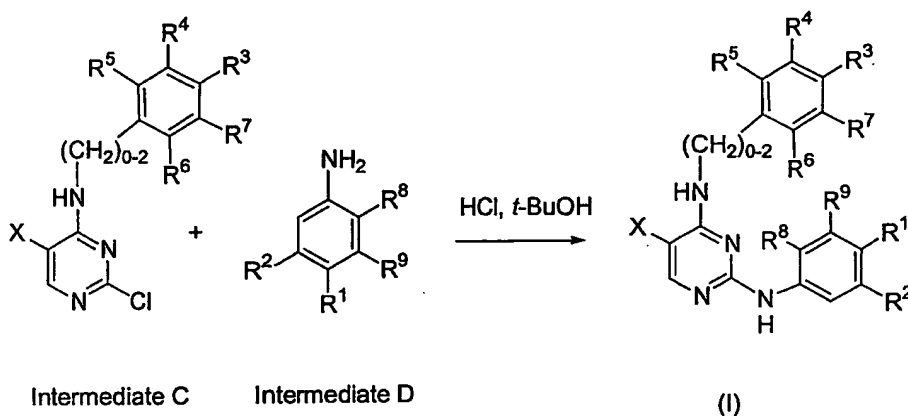
Unless the context clearly indicates to the contrary, whenever the term "compounds of this invention," "compounds of the present invention", and the like, are used herein, they are intended to include the chemically feasible pharmaceutically acceptable salts and/or esters as well as all stereoisomeric forms of the referenced compounds.

#### Method of making the compounds of the present invention

In general, the compounds used in this invention may be prepared by standard techniques known in the art, by known processes analogous thereto, and/or by the processes described herein, using starting materials which are either commercially available or producible according to routine, conventional chemical methods. The following preparative methods are presented as an example of the synthesis of the compounds of the present invention.

#### General Experimental Procedures

The compounds of this invention can be synthesized according to the general method of Reaction Scheme 1 described below.

Reaction Scheme 1General Method of Preparation of Compounds of Formula (I)Step 1.Step 2.

In Reaction Scheme 1, the  $R^1$ - $R^9$  and X groups have the same meaning as defined above for Formula I. In general, compounds of Formula (I) can be prepared in two steps. In the first step, a dichloropyrimidine, (Intermediate A), is allowed to react with an optionally substituted aniline or phenylalkylamine (Intermediate B) in the presence of a basic catalyst to give Intermediate C. In step two, Intermediate C is allowed to react with an aniline, represented as Intermediate D, in the presence of an acid catalyst.

Where Intermediates A or D are not commercially available, they may be prepared by methods well known in the art or by those methods specifically described below for the preparation of intermediates.

Using the above general methods, the specific procedures described below, together with the knowledge of one skilled in the art, all of compounds of Formula I may be prepared.

The following specific examples are presented to further illustrate the invention described herein, but they are not intended, nor should they be construed, to limit the scope of the invention in any way.

## 5      Abbreviations and Acronyms

When the following abbreviations are used herein, they have the following meaning:

	AcOH	acetic acid
	AgOTf	silver trifluoromethanesulfonate
	AlMe <sub>3</sub>	trimethylaluminum
10	abs	absolute
	AmmOH	Ammonium Hydroxide
	BH <sub>3</sub> ·THF	borane-tetrahydrofuran complex
	BOC	<i>tert</i> -butoxycarbonyl
	<i>n</i> -BuLi	butyllithium
15	<i>n</i> -BuOH	1-butanol
	<i>t</i> -BuOH	<i>tert</i> -butyl alcohol
	CBr <sub>4</sub>	carbon tetrabromide
	CD <sub>3</sub> OD	methanol- <i>d</i> <sub>4</sub>
	CDCl <sub>3</sub>	chloroform- <i>d</i>
20	Celite®	diatomaceous earth filtering agent, registered trademark of Celite Corp.
	DCE	1,2-dichloroethane
	dH <sub>2</sub> O	de-ionized water
	DMAP	4-dimethylaminopyridine
	DMF	<i>N,N</i> -dimethylformamide
25	DMSO	dimethylsulfoxide
	dppp	1,3-bis(diphenylphosphino)propane
	EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	equiv	equivalent(s)
	EPA vial	A 40 mL vial sold by Fisher Scientific and other common laboratory
30		supply vendors
	ESI-MS	electrospray ionization mass spectrometry
	Et <sub>3</sub> N	triethylamine
	EtOAc	ethyl acetate
	Et <sub>2</sub> O	diethyl ether
35	EtOH	ethanol

	HEPES	4-(2-hydroxyethyl)-1-piperazineethane-sulfonic acid
	HEX	hexanes
	<sup>1</sup> H NMR	proton nuclear magnetic resonance
	HPLC	high performance liquid chromatography
5	<i>i</i> -PA	<i>iso</i> -Propyl alcohol
	J-Kem Block	A parallel synthesis block sold by J-Kem, Inc.
	KOAc	potassium acetate
	KOH	potassium hydroxide
	LC/MS	liquid chromatography / mass spectroscopy
10	LiAlH <sub>4</sub>	lithium aluminum hydride
	<i>m</i> CPBA	3-chloroperoxybenzoic acid
	MeOH	methanol
	MMTV	murine mammary tumor virus
	MS ES	mass spectrometry with electrospray
15	NaBH(OAc) <sub>3</sub>	sodium triacetoxymborohydride
	NaCNBH <sub>3</sub>	sodium cyanoborohydride
	NaOAc	sodium acetate
	NaOH	sodium hydroxide
	NMM	<i>N</i> -methylmorpholine
20	Pd/C	palladium on carbon
	Pd(dppf)Cl <sub>2</sub>	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
	Pd(OAc) <sub>2</sub>	palladium (II) acetate
	Pd(PPh <sub>3</sub> ) <sub>4</sub>	tetrakis(triphenylphosphine)palladium(0)
	PS-NCO	polystyrene isocyanate
25	R <sub>f</sub>	TLC retention factor
	rt	room temperature
	SnCl <sub>2</sub>	tin (II) chloride
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
30	TMSCl	chlorotrimethylsilane
	TMSCN	trimethylsilyl cyanide
	TLC	thin layer chromatography
	RT	retention time (HPLC)

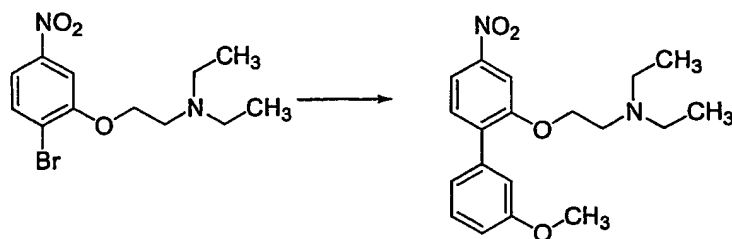
Unless otherwise stated, the term 'concentrated under reduced pressure' refers to use of a Buchi rotary evaporator at approximately 15 mm of Hg.

Thin-layer chromatography (TLC) was performed on Whatman® pre-coated glass-backed silica gel 60A F-254 250 µm plates. Visualization of plates was effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating, and/or (d) immersion of the plate in a cerium sulfate solution followed by heating. Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science® silica gel.

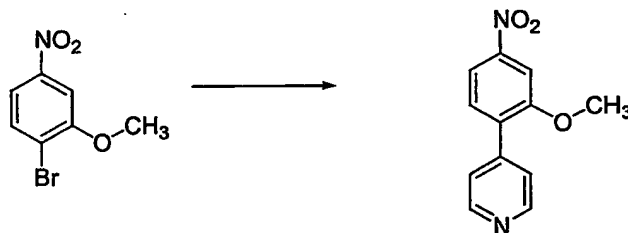
Proton (<sup>1</sup>H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric GN-Omega 300 (300 MHz) spectrometer with either Me<sub>4</sub>Si (δ 0.00) or residual protonated solvent (CHCl<sub>3</sub> δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard. Carbon (<sup>13</sup>C) NMR spectra were measured with a General Electric GN-Omega 300 (75 MHz) spectrometer with solvent (CDCl<sub>3</sub> δ 77.0; d<sub>3</sub>-MeOD; δ 49.0; d<sub>6</sub>-DMSO δ 39.5) as standard.

HPLC - electrospray mass spectra (HPLC ES-MS) for characterization were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluants were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flow rate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

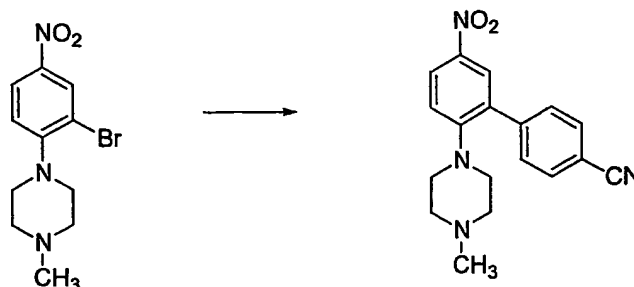
Preparative HPLC, when used, was run using either a Gilson 215 Liquid Handler with a Gilson 322 pump and a Gilson UV-VIS-155 detector set at 254 nm or a Shimadzu LC-8A pump with a Shimadzu SPD-10A detector set at 220 nM both equipped with a YMC Pac ProC18 column (150 x 20 mm). Alternatively, a YMC Pac ProC18 75 x 30 mm column was used with the Gilson HPLC. Eluant A is acetonitrile with 0.01% of trifluoroacetic acid and Eluant B is water with 0.01% trifluoroacetic acid. Typically, a gradient was run from 10% A / 90% B to 90%A / 10% B over a period of 15-25 min. The fractions of interest were collected and the solvent removed *in vacuo* to give the final compound as a trifluoroacetic acid salt.

Preparation of Nitroarene Starting MaterialsSynthetic Methods N1-N9Method N1Preparation of *N,N*-Diethyl-2-[(3'-methoxy-4-nitro-1,1'-biphenyl-2-yl)oxy]ethanamine

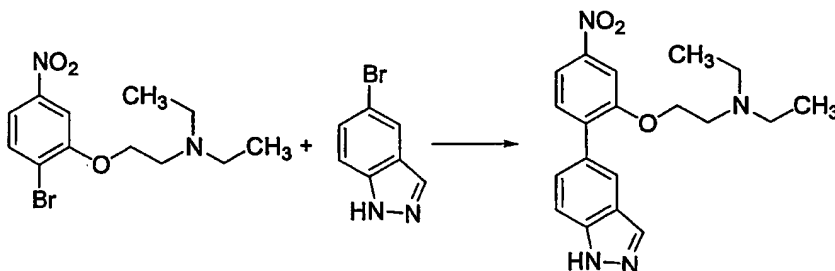
To a dry round-bottomed flask is added 4-bromo-3-(2-(diethylamino)ethoxy)-1-nitrobenzene (1 equiv), 3-methoxyphenylboronic acid (1.5 equiv), sodium bicarbonate (4 equiv), and (1,1-bis(diphenylphosphino)ferrocene)-dichloropalladium (0.1 equiv). 1,4-Dioxane (0.1M) is added and Ar is then bubbled through the solution for 15 minutes. Water (0.02M) is added and the reaction is heated at 90°C. After 16h the reaction mixture is cooled, diluted with ethyl acetate, and washed with saturated aqueous NaHCO<sub>3</sub> (1x) followed by H<sub>2</sub>O (1x). The organic layer is collected, condensed under reduced pressure, and purified by silica gel flash chromatography. LC/MS and <sup>1</sup>HNMR confirm the product.

Method N2Preparation of 4-(2-methoxy-4-nitrophenyl)pyridine

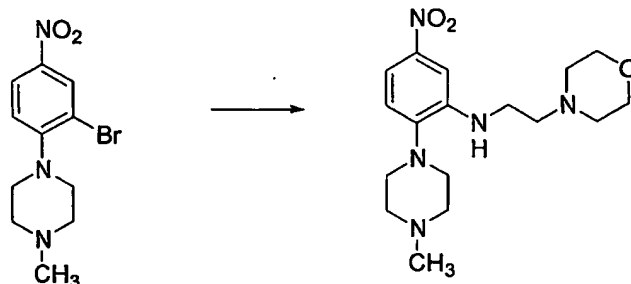
To a dry round-bottomed flask is added (bromo compound)(1 equiv), appropriate boronic acid (1.5 equiv), sodium bicarbonate (4 equiv), and (1,1-bis(diphenylphosphino)ferrocene)-dichloropalladium (0.1 equiv). 1,4-dioxane (0.1M) is added and Ar is then bubbled through the solution for 15 minutes. Water (0.02M) is added and the reaction is heated at 90°C. After 16h the reaction mixture is cooled, diluted with ethyl acetate, and washed with saturated aqueous NaHCO<sub>3</sub> (1x) followed by H<sub>2</sub>O (1x). The organic layer is collected, condensed under reduced pressure, and purified by silica gel flash chromatography. LC/MS and <sup>1</sup>HNMR confirm the product.

Method N3Preparation of 2'-(4-methyl-1-piperazinyl)-5'-nitro-1,1'-biphenyl-4-carbonitrile

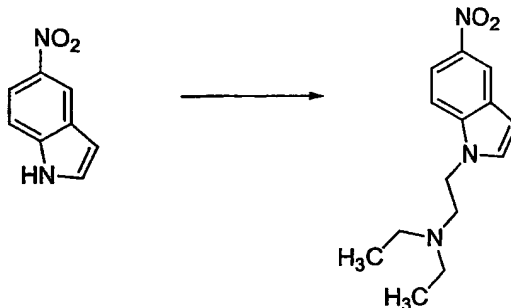
To a dry round-bottomed flask is added 1-methyl-4-(2-bromo-4-nitrophenyl)piperazine (1 equiv), 4-cyanophenylboronic acid (1.5 equiv), sodium bicarbonate (4 equiv), and (1,1-bis(diphenylphosphino)ferrocene)-dichloropalladium (0.1 equiv). 1,4-dioxane (0.1M) is added and Ar is then bubbled through the solution for 15 minutes. Water (0.02M) is added and the reaction is heated at 90°C. After 16h the reaction mixture is cooled, diluted with ethyl acetate, and washed with saturated aqueous NaHCO<sub>3</sub> (1x) followed by H<sub>2</sub>O (1x). The organic layer is collected, condensed under reduced pressure, and purified by silica gel flash chromatography. LC/MS and <sup>1</sup>HNMR confirm the product.

Method N4Preparation of *N,N*-diethyl-2-[2-(1*H*-indazol-5-yl)-5-nitrophenoxy]ethanamine

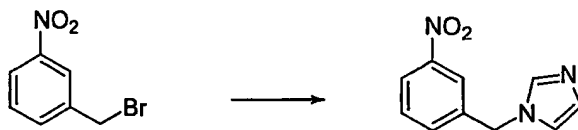
A two neck flask charged with the 5-bromo-1*H*-indazole (1 equiv), Pd(dppf)Cl<sub>2</sub> (0.03 equiv), KOAc (3 equiv) and bis(pinacolato)diboron (1.1 equiv) was flushed with Ar. DMF (0.25 M) was added via a syringe to form a red solution. The mixture was heated at 80 °C for 2h. After the reaction was cooled to rt, Pd(dppf)Cl<sub>2</sub> (0.03 equiv), the nitro bromide compound (1 equiv) and Na<sub>2</sub>CO<sub>3</sub> aqueous solution (1 M, 5 equiv) were added. The mixture was stirred under Ar at 80 °C overnight. The reaction mixture was allowed to cool to rt, extracted with EtOAc and washed with brine. The extract was then dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by flash silica column chromatography (EtOAc/MeOH=9:1) to afford the pure product which was confirmed by LC/MS and <sup>1</sup>H NMR.

Method N5Preparation of 2-(4-methyl-1-piperazinyl)-N-[2-(4-morpholinyl)ethyl]-5-nitroaniline

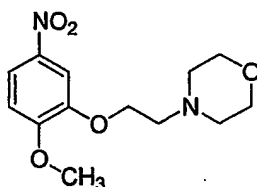
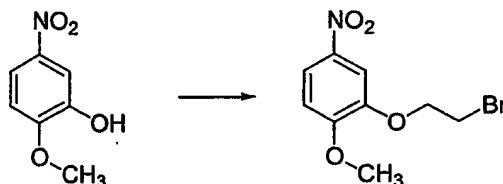
To a dry round-bottomed flask is added 1-methyl-4-(2-bromo-4-nitrophenyl)piperazine (1 equiv), 2-(4-morpholinyl)ethylamine (1.5 equiv), potassium *tert*-butoxide (1.4 equiv), *rac*-BINAP (0.2 equiv) and Pd<sub>2</sub>(dba)<sub>3</sub> (0.1 equiv). 1,4-Dioxane (0.1M) is added and Ar is then bubbled through the solution for 15 minutes. The reaction is heated at 80°C. After 8h the reaction mixture is cooled, diluted with ethyl acetate, filtered through a Celite<sup>®</sup> plug. The plug is washed well with EtOAc. The organic layer is collected, condensed under reduced pressure, and purified by silica gel flash chromatography. LC/MS and <sup>1</sup>HNMR confirm the product.

Method N6Preparation of *N,N*-diethyl-2-(5-nitro-1*H*-indol-1-yl)ethanamine

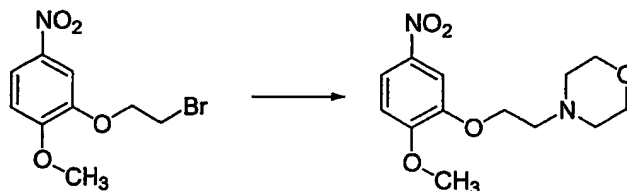
A slurry of 5-nitroindole (1 equiv) and NaOH pellets (1 equiv) in H<sub>2</sub>O (7 M) was stirred for 10 min after which time *p*-xylene (1.4 M), K<sub>2</sub>CO<sub>3</sub> (1.5 equiv) and corresponding alkyl halide (1 equiv) was added and the reaction heated to 100 °C for 4 h. The reaction was cooled to rt then concentrated under reduced pressure. The crude residue was dissolved in *p*-xylene and washed with 1N NaOH (2 x) and H<sub>2</sub>O (1 x). The organic layer was dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to furnish the resulting crude material that was confirmed by LC/MS and <sup>1</sup>H NMR.

Method N7Preparation of 1-(3-nitrobenzyl)-1H-imidazole

5 To a round-bottomed flask is added 3-nitrobenzyl bromide (1 equiv) followed by imidazole (2 equiv) in THF (0.4M). The solution is heated at 60 °C. After 16h the reaction mixture is cooled, diluted with ethyl acetate, and washed with saturated aqueous NaHCO<sub>3</sub> (1x) followed by H<sub>2</sub>O (1x). The organic layer is collected, condensed under reduced pressure, and purified by silica gel flash chromatography. LC/MS and <sup>1</sup>HNMR  
10 confirm the product.

Methods N8-N9Preparation of 4-[2-(2-methoxy-5-nitrophenoxy)ethyl]morpholineStep 1. Method N8 Preparation of 2-(2-bromoethoxy)-1-methoxy-4-nitrobenzene

15 A solution of 2-methoxy-5-nitrophenol (1 equiv) in CH<sub>3</sub>CN (0.72 M) was added 1,2-dibromoethane (1 equiv) and Cs<sub>2</sub>CO<sub>3</sub> (3 equiv). The mixture was refluxed overnight. After cooling to rt, the reaction mixture was diluted by EtOAc and washed with 1N NaOH (3x), water (1x) and brine (2x). The organic layer was dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to afford the crude product which was confirmed by <sup>1</sup>H NMR and used without  
20 further purification.

Step 2. Method N9 Preparation of 4-[2-(2-methoxy-5-nitrophenoxy)ethyl]morpholine

A solution of 3-(2-bromoethoxy)-4-methoxynitrobenzene (1 equiv), piperidine (2 equiv) and  $K_2CO_3$  (8 equiv) in acetone (0.10 M) was heated to 65 °C for 24 h. The reaction mixture was allowed to cool to rt, diluted with EtOAc and washed with  $H_2O$ . The organic layer was concentrated *in vacuo* and the resulting crude solid or oil was purified by silica gel column chromatography to furnish the intermediate nitro derivative which was confirmed by LC/MS and  $^1H$  NMR.

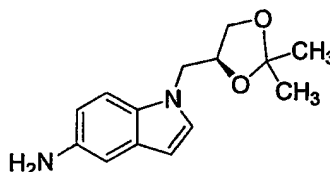
Preparation of Anilines: (Reactions Scheme I Intermediates B and D)

Synthetic Methods B1-B7 and D1

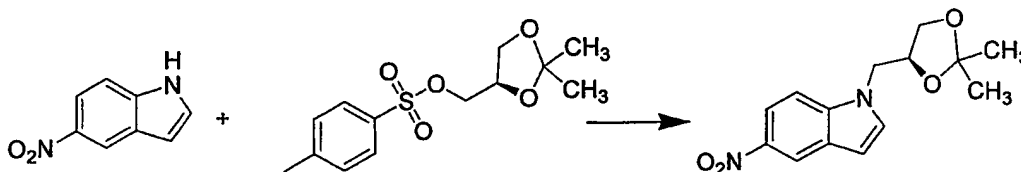
Intermediate B-1

Method B1

Preparation of 1-[[4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]-1H-indol-5-amine

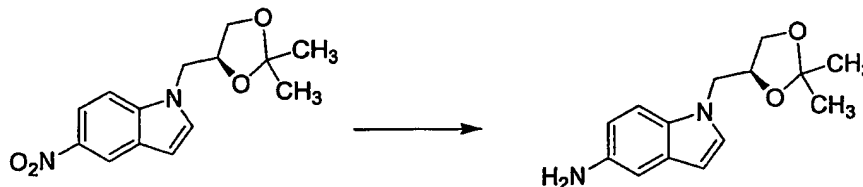


Step 1. Preparation of 1-[[4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]-5-nitro-1H-indole



The compound was prepared by reaction of 5-nitroindole (1.0 equiv) with [(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 4-methylbenzenesulfonate (5.0 equiv) in the presence of cesium carbonate (2.0 equiv) in DMF at 80 °C for 48 h. A similar procedure is described in more detail in Method 4 below.

Step 2. Method B1 Preparation of 1-[[4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]-1H-indol-5-amine



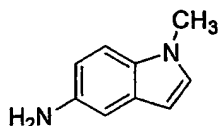
To 2.8 g (10 mmol, 1.0 equiv) 1-[[4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]-5-nitro-1H-indole in EtOH (100 mL) and THF (10 mL) was added 6.8 g (30 mmol, 3equiv) tin(II)chloride dihydrate and the reaction was heated to 100 °C for 24h. It was

concentrated, taken up in  $K_2CO_3$  and filtered through Celite®. The filtrate was extracted with EtOAc and the organic layers dried with  $MgSO_4$ , filtered and concentrated to 2.5 g (99%) 1-[[[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]-1H-indol-5-amine.

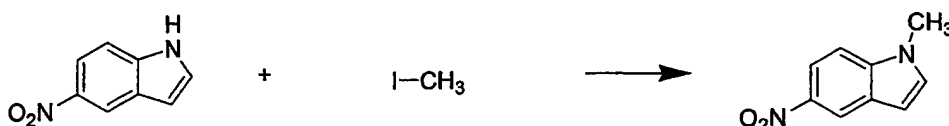
### Intermediate B-2

#### Methods B2a and B2b

#### Preparation of 1-methyl-5-amino-1H-indole

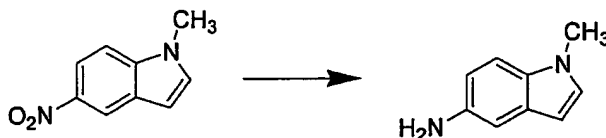


#### Step 1. Method B2a Preparation of 1-methyl-5-nitro-1H-indole



To 1.0 g (6 mmol, 1.0equiv) 5-nitroindole in acetone (12 mL) and  $H_2O$  (3 mL) was added KOH (1.0 g, 18 mmol) followed by iodomethane (0.75 mL, 12 mmol). The reaction was allowed to stir for 24 h then was filtered to yield 0.8 g (78%-98%) 1-methyl-5-nitro-1H-indole.

#### Step 2. Method B2b Preparation of 1-methyl-5-amino-1H-indole

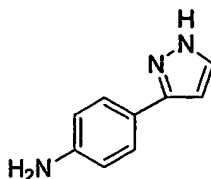


To 0.9 g (5mmol, 1.0equiv) 1-methyl-5-nitro-1H-indole in 10mL MeOH was added 0.01g 10% Pd/C (0.09mmol, 0.01equiv) and the reaction was stirred under 1atm hydrogen for 34 h. The reaction was filtered and concentrated to give 0.4g (43%-62%) 1-methyl-5-amino-1H-indole.

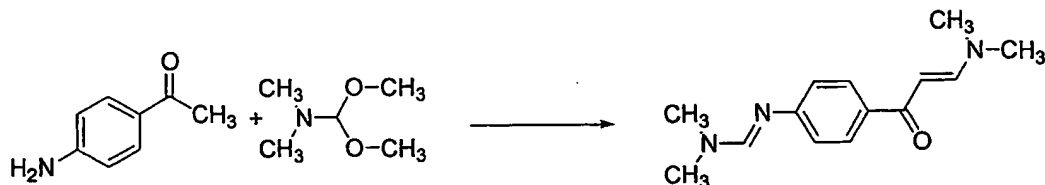
### Intermediate B-3

#### Method B3

#### Preparation of 4-aminophenyl-pyrazole

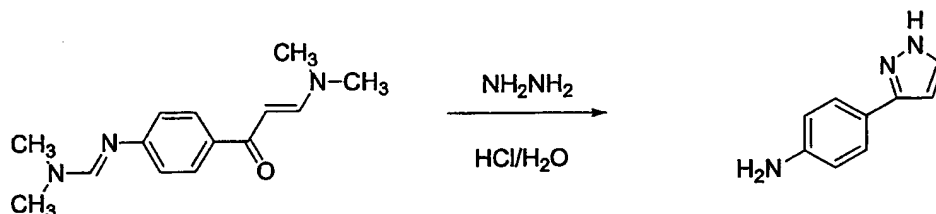


Step 1: Preparation of *N'*-[4-[(2*E*)-3-(dimethylamino)-2-propenoyl]phenyl]-*N,N*-dimethylimidoforamide



A mixture of 1-(4-amino-phenyl)-ethanone (10.0 g, 74 mmol) and dimethoxymethyl-dimethylamine (20.0 g, 156 mmol) was heated at 110 °C for 24 h, cooled to room temperature and concentrated under reduced pressure. The crude product was used in the next step without purification.

Step 2: Preparation of 4-aminophenyl-pyrazole

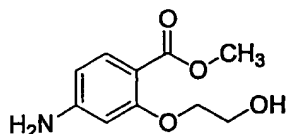


The crude product obtained from step one was treated with water (125.0 mL), 1N HCl (8.0 mL), and hydrazine monohydrate (7.4 g, 148 mmol). The mixture was heated at 110 °C for 18 h, cooled down to room temperature, neutralized with saturated NaHCO<sub>3</sub> solution (10.0 mL) and extracted with EtOAc (200 mL) three times. Combined the extract and dried over MgSO<sub>4</sub>, concentrated under reduced pressure to about 100 mL. 1N HCl in ether (74 mL) was added slowly while stirring vigorously. The precipitate was filtered and dried to give 11.5 g (80%) 4-aminophenyl-pyrazole hydrochloride as a yellow powder.

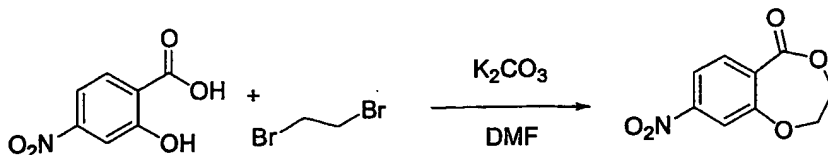
Intermediate B-4

Method B4

Preparation of methyl 4-amino-2-(2-hydroxyethoxy)benzoate



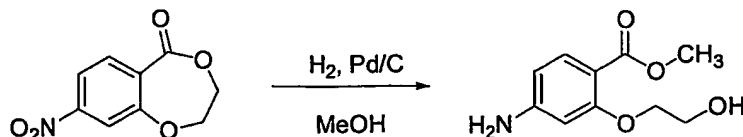
Step 1: Preparation of 8-nitro-2,3-dihydro-5*H*-1,4-benzodioxepin-5-one.



To a suspension of K<sub>2</sub>CO<sub>3</sub> (3.7 g, 27 mmol) in DMF (50 mL), were added 2-hydroxy-4-nitrobenzoic acid (2.0 g, 11 mmol) and dibromoethane (5.1g, 27 mmol). The

mixture was heated at 60 °C for 18 h then cooled down to room temperature and water (200 mL) was added. The product was precipitated, filtered, washed with EtOAc, and dried to give 1.0 g (51%) 8-nitro-2,3-dihydro-benzo[e][1,4]dioxepin-5-one as a pale yellow powder .

5 Step 2: Preparation of methyl 4-amino-2-(2-hydroxyethoxy)benzoate

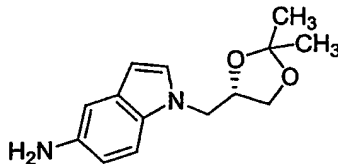


To a solution of 8-nitro-2,3-dihydro-benzo[e][1,4]dioxepin-5-one (1.0 g, 4.8 mmol) in MeOH and THF, were added 10% Pd/C (50 mg). The mixture was stirred under hydrogen atmosphere for 48 h. The mixture was filtered and concentrated under reduced pressure, the residue was diluted with 400 mL EtOAc and filtered again. Concentrated under reduced pressure to give 0.6 g (60%) 2-(2-hydroxy-ethoxy)-4-aminobenzoic acid methyl ester.

Intermediate B-5

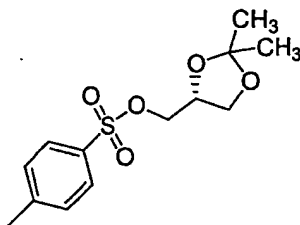
Method B5

15 Preparation of 1-((S)-2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-1H-indol-5-ylamine

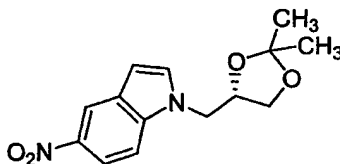


Step 1a. Toluene-4-sulfonic acid (S)-2,2-dimethyl-[1,3]dioxolan-4-yl methyl ester

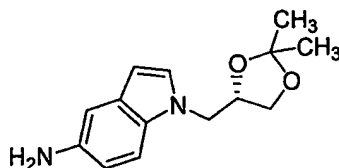
To a stirred solution of (*R*)-(-)-2,2-dimethyl-1,3-dioxolane-4-methanol (25 g; 0.19 mol) in anhydrous dichloromethane (153 mL) cooling under argon atmosphere in ice water was added, successively, triethylamine (28.4 mL; 0.2 mol), p-toluenesulfonyl chloride (39.27 g; 0.2 mol), and 4-dimethylaminopyridine (0.23 g; 1.9 mmol). The solution was stirred and allowed to warm to room temperature overnight, then was poured into a mixture of water (120 mL) and hexane (240 mL) stirring in ice water. The 2-phase mixture was poured into a separatory funnel, the phases separated, and the organic phase washed successively with water (75 mL), then brine (75 mL) before drying over anhydrous sodium sulfate. Filtration and concentration in vacuo afforded toluene-4-sulfonic acid (S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester as a thick yellow oil; <sup>1</sup>H NMR shows the presence of residual p-toluenesulfonyl chloride. <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>) δ 7.7 (d, 2H), 7.4 (d, 2H), 4.2 (m, 1H), 4.01 (dd, 1H), 3.97 (d, 2H), 3.7 (dd, 1H), 2.5 (s, 3H), 1.32 (s, 3H), 1.3 (d, 3H).

Step 1b. Toluene-4-sulfonic acid (*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester

To a stirred solution of (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol (20 g; 0.15 mol) in anhydrous dichloromethane (125 mL) cooling under argon atmosphere in ice water was added, successively, triethylamine (23 mL; 0.16 mol), p-toluenesulfonyl chloride (39.27 g; 0.16 mol), and 4-dimethylaminopyridine (0.23 g; 1.6 mmol). The solution was stirred and allowed to warm to room temperature; after 7 h the reaction was poured into a stirred mixture of water (125 mL) and hexane (250 mL). The 2-phase mixture was poured into a separatory funnel, the phases separated, and the organic phase washed successively with water (75 mL), then brine (75 mL) before drying over anhydrous sodium sulfate. Filtration and concentration in vacuo afforded toluene-4-sulfonic acid (*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester as a thick yellow oil; <sup>1</sup>H NMR shows the presence of residual p-toluenesulfonyl chloride. <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>): 7.7δ (d, 2H), 7.4δ (d, 2H), 4.2δ (m, 1H), 4.01δ (dd, 1H), 3.97δ (d, 2H), 3.7δ (dd, 1H), 2.5δ (s, 3H), 1.32δ (s, 3H), 1.3δ (d, 3H).

Step 2. 1-((*S*)-2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-5-nitro-1*H*-indole

To a stirred solution of 5-nitroindole (10.41 g; 63.6 mmol) and toluene-4-sulfonic acid (*S*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester (21.85 g; 76.3 mmol) in anhydrous *N,N*-dimethylformamide (100 mL) was added cesium carbonate (41.86 g; 127.2 mmol), and the mixture stirred overnight under argon at 80°C. After allowing the mixture to cool to room temperature, it was poured into a stirred mixture of hexanes and ethyl acetate (200 mL each). The solids were filtered off and washed with more solvent. The filtrate was washed with water and brine (250 mL each) before drying (anhydrous sodium sulfate); filtration and concentration in vacuo afforded the theoretical weight of 1-((*S*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-5-nitro-1*H*-indole as a cloudy orange oil. TLC: *R*<sub>f</sub> 0.3 (50% EtOAc/hexanes), *R*<sub>f</sub> 0.6 (5% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>): 8.6δ (d, 1H), 8.1δ (dd, 1H), 7.4δ (d, 1H), 7.3δ (d, 1H), 6.7δ (dd, 1H), 4.4δ (m, 1H), 4.3δ (dd, 1H), 4.2δ (dd, 1H), 4.1δ (dd, 1H), 3.7δ (dd, 1H), 1.4δ (s, 3H), 1.3δ (d, 3H).



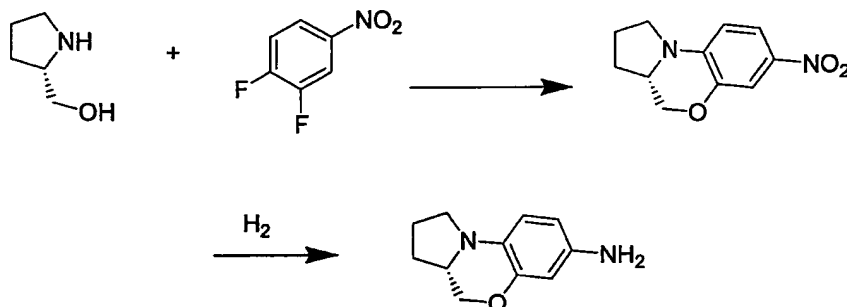
Step 3. 1-((S)-2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl)-1H-indol-5-ylamine

To a solution of 1-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-5-nitro-1H-indole in ethyl acetate and ethanol (50 mL each) was added 5% palladium on carbon (Degussa type), and the mixture stirred overnight at room temperature under an atmosphere of hydrogen. The mixture was filtered through Celite® and concentrated in vacuo to afford the theoretical weight of 1-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-1H-indol-5-ylamine as a dark red gum. TLC:  $R_f$  0.18 (50% EtOAc/hexanes);  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ ): 7.28 (m, 1H), 7.18 (d, 1H), 6.98 (dd, 1H), 6.68 (m, 1H), 6.38 (dd, 1H), 5.38 (dd, 1H), 4.48 (m, 1H), 4.18 (dd, 2H), 4.08 (dd, 1H), 3.78 (dd, 1H), 3.58 (broad exchangeable s, 2H), 1.48 (d, 3H), 1.38 (d, 3H).

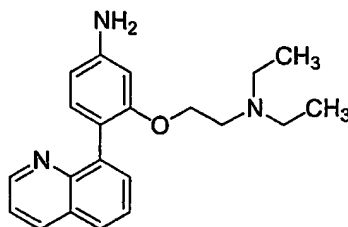
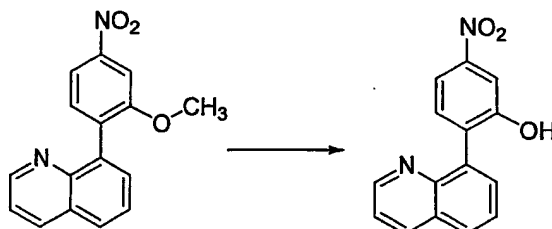
Intermediate B-6

Method B6

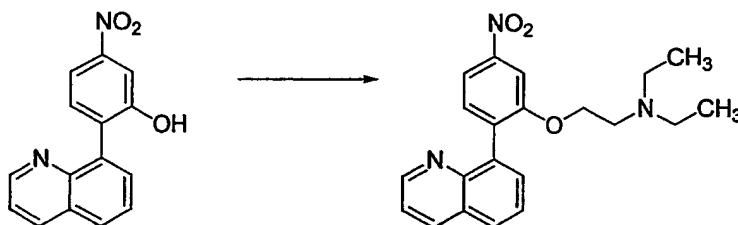
Preparation of (3aS)-2,3,3a,4-tetrahydro-1H-pyrrolo[2,1-c][1,4]benzoxazin-7-amine



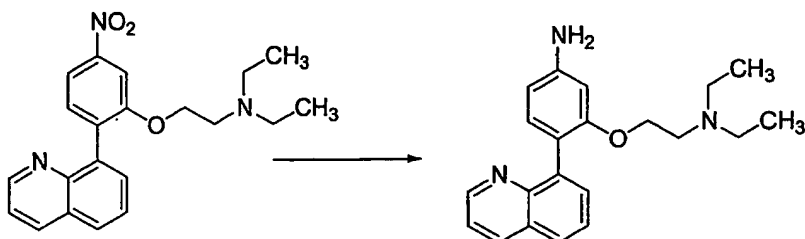
(S)-Prolinol (1 equiv) and 3,4-difluoronitroaniline (1 equiv) were combined with DMSO followed by addition of KOH (2.45 equiv) and heated to 100 °C for 18 h. Then, the mixture was acidified and then filtered. Next, the crude solution was then subjected to the hydrogenation procedure as described above for Method B7c.

Intermediate B-7Methods B7a, B7b, B7cPreparation of 3-[2-(Diethylamino)ethoxy]-4-(8-quinoliny)aniline5 Step 1. Method B7a Demethylation of 1-methoxy-3-nitrophenols using hydrogen bromide

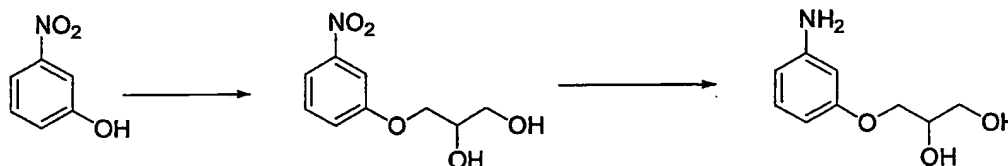
To a solution of 48% HBr (0.5 M) was added 2-(8-quinoliny)-5-nitroanisole (1 equiv). The solution was heated at reflux for 3 days. The reaction mixture was allowed to cool to rt, diluted with H<sub>2</sub>O, and extracted with EtOAc. The organic layer was dried  
 10 (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to give crude organic residue. Purification by silica gel column chromatography using 20%EtOAc/80%Hex as eluent, afforded the intermediate phenol which was confirmed by LC/MS and <sup>1</sup>H NMR.

Step 2. Method B7b Preparation of 2-phenoxy ethylamines

A slurry of 2-(8-quinoliny)-5-nitrophenol (1 equiv) and NaOH pellets (1 equiv) in H<sub>2</sub>O (7 M) was stirred for 10 min after which time *p*-xylene (1.4 M), K<sub>2</sub>CO<sub>3</sub> (1.5 equiv) and aminoethylchloride·HCl (1 equiv) was added and the reaction heated to 100 °C for 4 h. The reaction was cooled to rt then concentrated under reduced pressure. The crude residue was dissolved in *p*-xylene and washed with 1N NaOH (2 x) and H<sub>2</sub>O (1 x). The  
 20 organic layer was dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to furnish the resulting crude material which was confirmed by LC/MS and <sup>1</sup>H NMR.

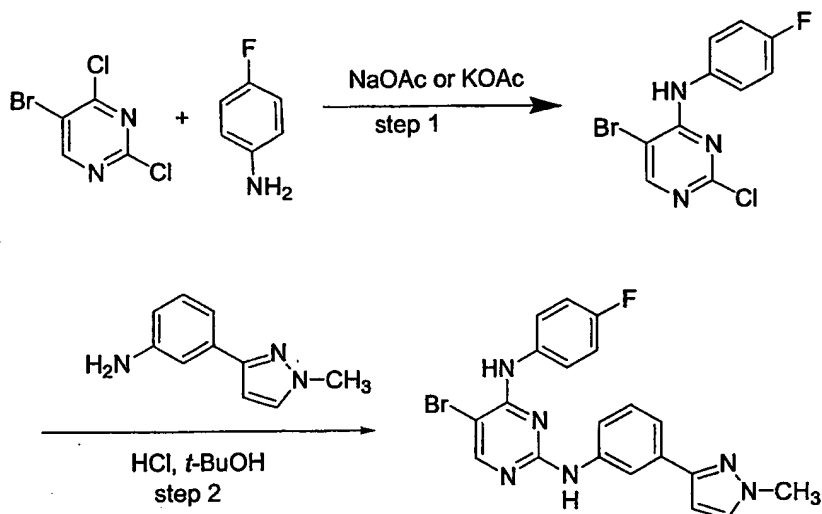
Step 3. Method B7c Reduction of nitrophenols to anilines using Pd/C

A solution of 4-(8-quinolinyl)-3-(2-(diethylamino)ethoxy)nitrophenol in EtOH (0.2 M) was added via syringe to a flask containing Palladium on carbon (10 mol%). The reaction vessel was fitted with a balloon adapter and charged with hydrogen and evacuated three times until the reaction was under a H<sub>2</sub> atmosphere. The reaction was allowed to stir overnight and then purged with Ar and evacuated three times until an Ar atmosphere had been achieved. The reaction solution was filtered through a pad of Celite® and washed with copious amounts of EtOH. The filtrate was concentrated *in vacuo* to afford the desired aniline which was confirmed by LC/MS and <sup>1</sup>H NMR.

Intermediate D-1Method D1Preparation of 3-(3-Aminophenoxy)-1,2-propanediol

**Step 1.** To 3-nitrophenol (10.00 g, 7 mmol) in EtOH (50 mL) was added sodium hydroxide (3.59 g, 9 mmol) in water (4 mL) and the reaction was heated to 80 °C for 10 min. To this was added 3-chloro-1,2-propanediol (3.59 g, 9 mmol) and the reaction was stirred at 80 °C for 18 h. It was then allowed to cool to room temperature, taken up in EtOAc, washed with 1N NaOH, washed with brine, dried with MgSO<sub>4</sub>, filtered and concentrated to give 14.92 g of 3-(3-nitrophenoxy)-1,2-propanediol (97%).

**Step 2.** To 3-(3-nitrophenoxy)-1,2-propanediol (14.92 g, 70 mmol) in ethanol (560 mL) was added tin (II) chloride dihydrate (63.17g, 280 mmol) and the reaction heated to 100 °C for 18 h. It was cooled and concentrated. The yellow oil was taken up in EtOAc and quenched with K<sub>2</sub>CO<sub>3</sub> to pH=12, filtered, and then extracted with additional EtOAc to give 6.26 g of 3-(3-aminophenoxy)-1,2-propanediol as a yellow oil (49%).

Preparation of Specific Compounds of the InventionExample 1Methods 1a, 1b, 1c, and 1dPreparation of *N*-[5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl]-*N*-[3-(1-methyl-1*H*-pyrazol-3-yl)phenyl]amine

10 Step 1. Two methods were used:

Method 1a. To a solution of NaOAc (27.0 g, 330 mmol) in water (70 mL) and THF (140 mL), were added 5-bromo-2,4-dichloropyrimidine (25.0 g, 110 mmol) and 4-fluoroaniline (12.2 g, 110 mmol). The mixture was stirred at room temperature for 18 h then saturated NaHCO<sub>3</sub> solution (50 mL) was added and the aqueous layer was  
 15 extracted with EtOAc (150 mL × 2); the combined organic layers were dried over MgSO<sub>4</sub>; filtered and concentrated under reduced pressure. The residue was treated with 200 mL hexane and filtered to give 5-bromo-2-chloro-4-[(4-fluorophenyl)amino]-pyrimidine as a 30.0 g pale yellow powder (90%).

Method 1b. To a solution of K<sub>2</sub>CO<sub>3</sub> (44.5 g, 322 mmol) in water (125 mL) and *i*-PA (375 mL), were added 5-bromo-2,4-dichloropyrimidine (25.0 g, 108 mmol) and 4-fluoroaniline (12.0 g, 107 mmol). The mixture was stirred at room temperature for 18 h then water (3000 mL) was added and the product was precipitated out. Filtered and dried  
 20 to give 30.0 g (90%) 5-bromo-2-chloro-4-[(4-fluorophenyl)amino]-pyrimidine as a pale yellow powder.

25

Step 2.

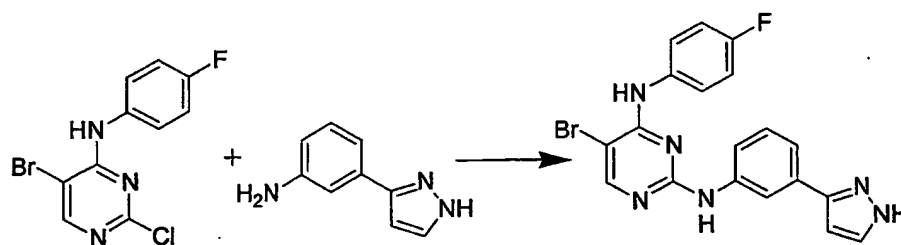
Method 1c To a solution of 5-bromo-2-chloro-4-[(4-fluorophenyl)amino]-pyrimidine (0.85 g, 2.8 mmol) and 3-(1-methyl-1*H*-pyrazol-3-yl)-phenyl amine (0.49 g, 2.8 mmol) in *t*-BuOH (25 mL) was added concentrated HCl (0.1 mL). The mixture was heated to 100 °C for 18 h, and then cooled down to room temperature. The precipitate was filtered and dried *in vacuo* to give 0.95 g (71%) desired product (HCl salt). ESI-LC/MS *m/e* calculated for C<sub>19</sub>H<sub>14</sub>BrFN<sub>6</sub>: 424.0; Found: 425.3 (M+1)<sup>+</sup>; R<sub>f</sub> = 0.40 (EtOAc/Hex=1/1).

Combined Steps 1 and 2.

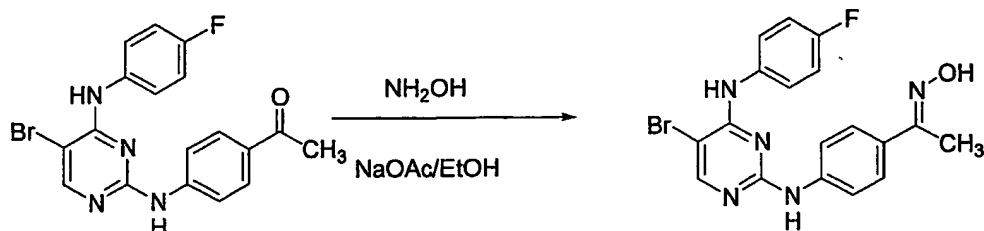
Method 1d. In a 40 mL EPA vial, 100 mg (1 equivalent) of the 4-substituted pyrimidine intermediate was mixed with the calculated amount of amine (2 equivalent) in 2 mL 1N HCl. The reaction mixture was capped and heated at 100 °C in a J-Kem Block with shaking for 1 or 2 days. After the reaction was completed, DMSO was added into the reaction mixture to dissolve all of the precipitate, then Et<sub>3</sub>N was added dropwise until the mixture was basic. After these steps, the mixture was purified by preparative HPLC.

Example 2Method 2

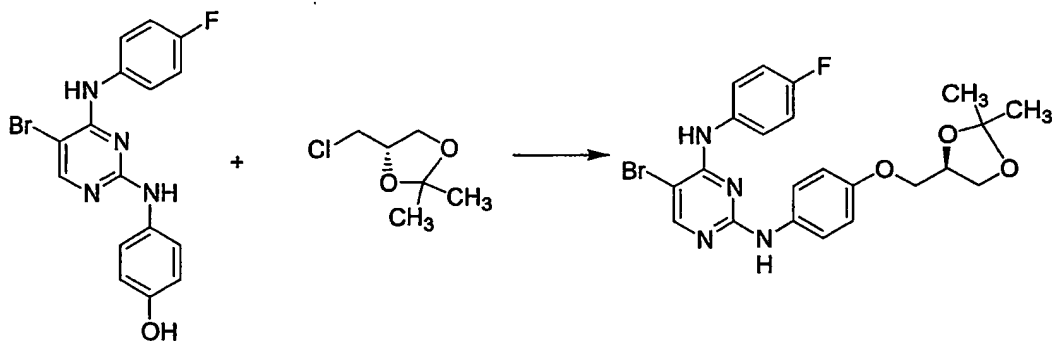
Preparation of *N*-(5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)-*N*-[3-(1*H*-pyrazol-3-yl)phenyl]amine



To a solution of 5-bromo-2-chloro-4-(4-fluoroanilino)pyrimidine (4.0 g, 13.2 mmol) and 3-(3-aminophenyl)-1*H*-pyrazole (2.3 g, 14.5 mmol) in dioxane (75 mL) was added 1 N HCl (75 mL). The mixture was heated to 100 °C for 18 h, and then cooled down to room temperature. Sodium bicarbonate (8.4 g, 100 mmol) was added in several portions while stirring. The precipitate was filtered and dried *in vacuo* to give 3.87 g (69%) desired product. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.16 (s, 1H), 7.80 (m, 1H), 7.67 (d, 1H), 7.56 (m, 1H), 7.48 (dd, 2H), 7.31 (m, 2H), 6.92 (t, 2H), 6.56 (d, 1H); ESI-LC/MS *m/e* calculated for C<sub>19</sub>H<sub>14</sub>BrFN<sub>6</sub>: 424.0; Found: 425.3 (M+1)<sup>+</sup>; R<sub>f</sub> = 0.70 (EtOAc).

Example 3Method 3Preparation of (1E)-1-[4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenyl]ethanone oxime

To a suspension of 1-[4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenyl]ethanone (HCl salt, 90 mg, 0.21 mmol) and NaOAc (67 mg, 0.82 mmol) in EtOH (4.0 mL) was added Hydroxylamine hydrochloride (43 mg, 0.62 mmol). The mixture was heated to 100 °C for 18 h, and then cooled down to room temperature. Water (20 mL) was added while stirring; the precipitate was filtered and washed with water; dried in vacuo to give 61 mg (71%) of (1E)-1-[4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenyl]ethanone oxime. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.10 (s, 1H), 7.55 (dd, 2H), 7.51 (d, 2H), 7.44 (d, 2H), 7.11 (t, 2H), 2.21 (s, 3H); ESI-LC/MS m/e calculated for C<sub>18</sub>H<sub>15</sub>BrFN<sub>5</sub>O: 415.0; Found: 416.2 (M+1)<sup>+</sup>; R<sub>f</sub> = 0.54 (EtOAc/hex=1/1).

Example 4Method 4Preparation of N-[5-bromo-2-[(4-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy)phenyl]amino]-4-pyrimidinyl]-N-(4-fluorophenyl)amine

To 10.0g (30mmol, 1.0 equiv) 4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenol in 200mL DMF (moist) was added 20.1g (130 mmol, 5.0equiv) (4S)-4-(chloromethyl)-2,2-dimethyl-1,3-dioxolane and 17.4g (50 mmol, 2.0equiv) cesium carbonate and the mixture was heated to 80 °C for 48 h. The reaction was cooled, taken up in EtOAc and washed with a saturated solution of ammonium chloride (3x200 mL).

The organic layers were dried with  $\text{MgSO}_4$ , filtered and concentrated. This was purified by flash column chromatography (0 then 50% EtOAc/Hex) on alumina to yield 4.8 g (5% to 98%) *N*-{5-bromo-2-[(4-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy)phenyl]amino}-4-pyrimidinyl}-*N*-(4-fluorophenyl)amine.

5

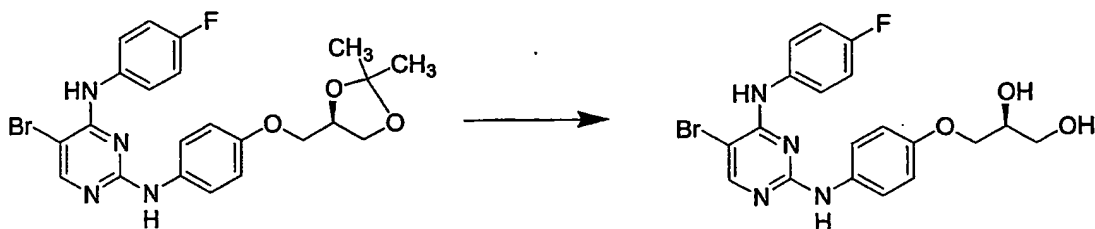
The above procedure was also used to make 1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl-5-nitro-1*H*-indole using 5-nitroindole and *R*(*D*)-2,2-dimethyl-1,3-dioxolane-4-methanol toluene-4-sulfonate. Yields 90-99%.

#### Example 5

##### Method 5

10

#### Preparation of (2*S*)-3-[4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenoxy]-1,2-propanediol



15

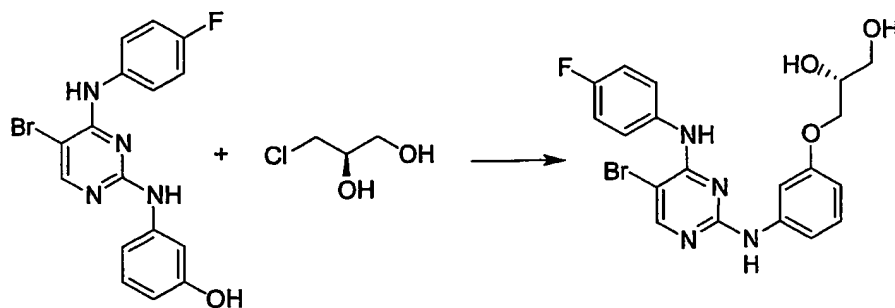
To 4.8 g (10 mmol, 1.0 equiv) *N*-{5-bromo-2-[(4-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy)phenyl]amino}-4-pyrimidinyl}-*N*-(4-fluorophenyl)amine in 90 mL MeOH/ $\text{CH}_2\text{Cl}_2$  (1:1) was added conc. HCl (2.3 mL) and the reaction was allowed to stir for 2 h. The reaction was treated with sat.  $\text{NaHCO}_3$  to pH=7 and extracted with *i*-PA/ $\text{CHCl}_3$  (1:3) to give 1.5 g (28-98%) (2*S*)-3-[4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenoxy]-1,2-propanediol.

20

#### Example 6

##### Method 6

#### Preparation of (2*R*)-3-[3-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenoxy]-1,2-propanediol



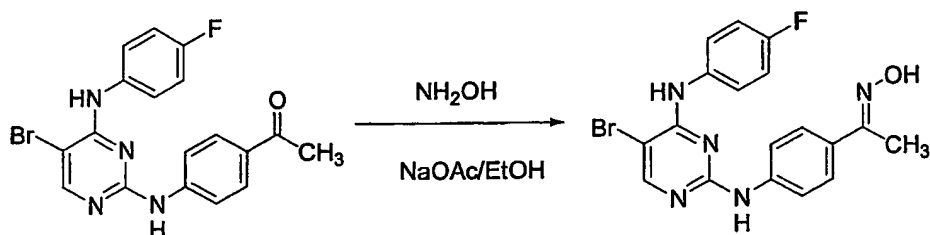
25

To 0.5g (0.1mmol, 1.0equiv) 3-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenol in 2.5mL EtOH was added 0.07g NaOH (2mmol, 1.25equiv) in 1mL H<sub>2</sub>O and the reaction was heated to 80°C for 1 h. To this was added 0.2g (2R)-3-chloro-1,2-propanediol (2mmol, 1.2equiv) and the reaction continued to heat at 80°C for 24 h. It was cooled and treated with 1N HCl to pH=7 and extracted with EtOAc. The organic layers were dried with MgSO<sub>4</sub>, filtered and concentrated. This was taken up in MeOH and filtered to yield 0.3g (2R)-3-[3-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenoxy]-1,2-propanediol (43%-61%).

### Example 3

#### Method 7

#### Preparation of (1E)-1-[4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenyl]ethanone oxime

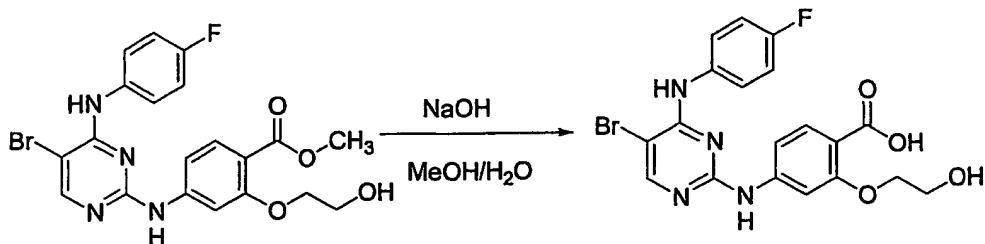


To a suspension of 1-[4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenyl]ethanone (HCl salt, 90 mg, 0.21 mmol) and NaOAc (67 mg, 0.82 mmol) in EtOH (4.0 mL) was added hydroxylamine hydrochloride (43 mg, 0.62 mmol). The mixture was heated to 100 °C for 18 h, and then cooled down to room temperature. Water (20 mL) was added while stirring; the precipitate was filtered and washed with water; dried *in vacuo* to give 61 mg (71%) of (1E)-1-[4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)phenyl]ethanone oxime. <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.10 (s, 1H), 7.55 (dd, 2H), 7.51 (d, 2H), 7.44 (d, 2H), 7.11 (t, 2H), 2.21 (s, 3H); ESI-LC/MS m/e calculated for C<sub>18</sub>H<sub>15</sub>BrFN<sub>5</sub>O: 415.0; Found: 416.2 (M+1)<sup>+</sup>; R<sub>f</sub> = 0.54 (EtOAc/hex=1/1).

### Example 8

#### Method 8

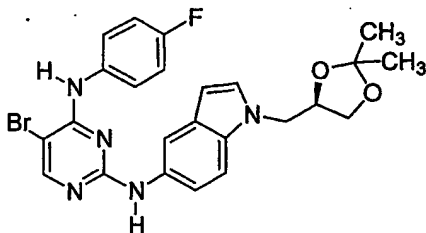
#### Preparation of 4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2-(2-hydroxyethoxy)benzoic acid



A suspension of 4-[5-bromo-4-(4-fluoro-phenylamino)-pyrimidin-2-ylamino]-2-(2-hydroxy-ethoxy)-benzoic acid methyl ester (3.7 g, 27 mmol) in MeOH (5.0 mL) and 1N NaOH (5.0 mL) was heated at 60 °C for 18 h then cooled down to room temperature and neutralized with 1N HCl (5.0 mL). Extracted with EtOAc, dried over MgSO<sub>4</sub>, concentrated to give 85 mg (87%) 4-[5-bromo-4-(4-fluoro-phenylamino)-pyrimidin-2-ylamino]-2-(2-hydroxy-ethoxy)-benzoic acid.

### Example 9

#### Preparation of 5-Bromo-*N*<sup>2</sup>-[1-((*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-1*H*-indol-5-yl]-*N*<sup>4</sup>-(4-fluoro-phenyl)-pyrimidine-2,4-diamine



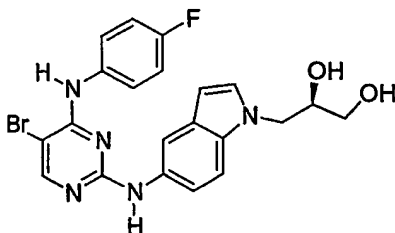
To a solution of 1-((*S*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-1*H*-indol-5-ylamine (5.38 g; 21.8 mmol) in *n*-butanol (20 mL) was added (5-bromo-2-chloro-pyrimidin-4-yl)-(4-fluorophenyl)amine (6.61 g; 21.8 mmol) and 1 drop of concentrated hydrochloric acid, and the stirred mixture heated in an oil bath to reflux. After 5 minutes the bath was lowered and the mixture allowed to cool to room temperature. The solid was filtered off, triturated and washed with diethyl ether to afford a mixture of 2 products, 5-bromo-*N*<sup>2</sup>-[1-((*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-1*H*-indol-5-yl]-*N*<sup>4</sup>-(4-fluoro-phenyl)-pyrimidine-2,4-diamine and (*R*)-3-[5-[5-bromo-4-(4-fluoro-phenylamino)-pyrimidin-2-ylamino]-indol-1-yl]-propane-1,2-diol, as hydrochloride salts. The solid was vigorously stirred in a mixture of ethyl acetate (300 mL) and water (100 mL), sodium bicarbonate (2 g; 23.8 mmol) was added, and the mixture stirred until no undissolved solid remained. The 2-phase mixture was poured into a separatory funnel, the phases separated, and the organic phase washed with brine (100 mL) before drying over anhydrous sodium sulfate. Filtration and concentration in vacuo afforded solid, which was triturated and washed with dichloromethane; the filtrate was applied to a column of silica gel. The column was eluted with dichloromethane, then a methanol/ dichloromethane solvent gradient (1-5%). The purest (by TLC) of 2 fractions was concentrated in vacuo, and the solid triturated with 50% dichloromethane/hexanes, filtered off and washed with more solvent. After drying in vacuo, there was obtained 0.82 g of 5-bromo-*N*<sup>2</sup>-[1-((*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-1*H*-indol-5-yl]-*N*<sup>4</sup>-(4-fluoro-phenyl)-pyrimidine-2,4-diamine as a colorless solid, mp 130 – 132°C; TLC: *R*<sub>f</sub> 0.28 (50% EtOAc/hexanes); <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>): 8.1δ (s, 1H),

7.8δ (d, 1H), 7.6δ (m, 2H), 7.3δ (d, 1H), 7.2δ (m, 1H), 7.1δ (broad s, 1H), 7.0δ (m, 3H), 4.4δ (m, 1H), 4.2δ (dd, 2H), 4.0δ (dd, 1H), 3.7δ (dd, 1H), 1.4δ (s, 3H), 1.3δ (s, 3H); LCMS  $m/z$  512 + 514 ( $M+H^+$ ), RT = 2.6 min. Anal. Calcd. for  $C_{24}H_{23}BrFN_5O_2$ : C, 56.26; H, 4.52; N, 13.67. Found: C, 55.96; H, 4.22; N, 13.66. The remaining fraction was concentrated in vacuo, and the solid triturated with 25% dichloromethane/hexanes to afford another 3.55 g (4.37 g total, 39%) of pure 5-bromo- $N^2$ -[1-((*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-1*H*-indol-5-yl]- $N^4$ -(4-fluoro-phenyl)-pyrimidine-2,4-diamine.

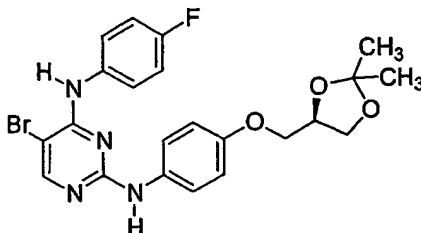
#### Example 10

#### Method 10

#### Preparation of (*R*)-3-[5-[5-Bromo-4-(4-fluoro-phenylamino)-pyrimidin-2-ylamino]-indol-1-yl]-propane-1,2-diol



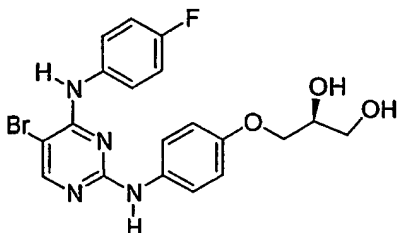
To a stirred mixture of 5-bromo- $N^2$ -[1-((*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-1*H*-indol-5-yl]- $N^4$ -(4-fluoro-phenyl)-pyrimidine-2,4-diamine (15.36 g; 30.0 mmol) in methanol (500 mL) was added 1N hydrochloric acid (120 mL); the stirred suspension was heated to 60 °C. After 30 minutes the mixture was allowed to cool to room temperature; the solid was filtered off, washed with methanol and dried. The solid was vigorously stirred in water containing sodium bicarbonate (4.1 g; 48.8 mmol); the resulting solid was filtered off, washed with water, ethanol and hexanes, then dried to afford 10.3 g (73%) of (*R*)-3-[5-[5-bromo-4-(4-fluoro-phenylamino)-pyrimidin-2-ylamino]-indol-1-yl]-propane-1,2-diol as a colorless solid, mp 206.5 – 209 °C.  $^1H$  NMR ( $DMSO-d_6$ ): 9.1δ (broad, exchangeable s, 1H), 8.5δ (broad, exchangeable s, 1H), 8.1δ (s, 1H), 7.8δ (d, 1H), 7.6δ (t, 2H), 7.3δ (d, 1H), 7.2δ (d, 1H), 7.1δ (m, 3H), 6.2δ (d, 1H), 4.9δ (exchangeable d, 1H), 4.7δ (exchangeable t, 1H), 4.2δ (dd, 1H), 4.0δ (dd, 1H), 3.7δ (m, 1H), 3.3δ (m, 1H), 3.2δ (m, 1H); LCMS  $m/z$  472 + 474 ( $M+H^+$ ), RT = 2.0 min. Anal. Calcd. for  $C_{21}H_{19}BrFN_5O_2$ : C, 53.4; H, 4.05; N, 14.83. Found: C, 53.38; H, 4.09; N, 14.85; chiral HPLC (CHIRALPAK AD-H, 4.6 X 250 mm., 1.0 mL/min., 280 nm, hexane + 0.1% TFA/ isopropanol + 0.1% TFA gradient):RT = 12.0 min., ee >98%.

Example 4Method 115-Bromo-*N*<sup>2</sup>-[4-((*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-*N*<sup>4</sup>-(4-fluoro-phenyl)-pyrimidine-2,4-diamine

A stirred suspension of 4-[5-bromo-4-(4-fluoro-phenylamino)-pyrimidin-2-ylamino]-phenol (11.3 g; 30.0 mmol), toluene-4-sulfonic acid (*S*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester (17.1 g; 60.0 mmol) and cesium carbonate (34.39 g; 100 mmol) in anhydrous *N,N*-dimethylformamide (120 mL) was heated under argon atmosphere at 90 °C for 1 hour, then allowed to cool to room temperature. The reaction mixture was partitioned between ethyl acetate (250 mL) and brine (500 mL), the phases separated, and the aqueous phase extracted with ethyl acetate (2 X 125 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried (anhydrous sodium sulfate), filtered and concentrated in vacuo to afford crude product. Purification by column chromatography on silica gel (hexane/ dichloromethane/ ethyl acetate solvent gradient) afforded 5-bromo-*N*<sup>2</sup>-[4-((*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-*N*<sup>4</sup>-(4-fluoro-phenyl)-pyrimidine-2,4-diamine as a pastel orange solid (10.57 g; 72%). A sample purified further (colorless solid, mp 119-122° C) gave the following data: TLC: *R*<sub>f</sub> 0.5 (25% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>): 8.1δ (s, 1H), 7.5δ (m, 2H), 7.4δ (m, 2H), 7.1δ (m, 4H), 6.8δ (m, 2H), 4.4δ (m, 1H), 4.1δ (dd, 1 H), 4.0δ (dd, 1H), 3.9δ (dd, 1 H), 3.8δ (dd, 1 H), 1.45 (d, 3H), 1.4 (d, 3H); LCMS *m/z* 489 + 491 (M+H<sup>+</sup>), RT = 2.6 min.; Anal. Calcd. for C<sub>22</sub>H<sub>22</sub>BrFN<sub>4</sub>O<sub>3</sub>: C, 54.0; H, 4.53; N, 11.45. Found: C, 53.98; H, 4.55; N, 11.21.

Example 5Method 12

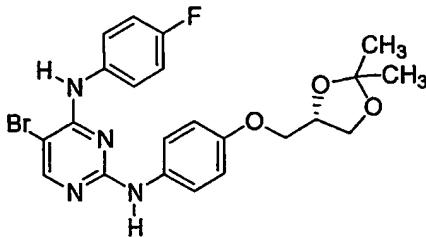
(S)-3-{4-[5-Bromo-4-(4-fluoro-phenylamino)-pyrimidin-2-ylamino]-phenoxy}-propane-1,2-  
diol



Trifluoroacetic acid (150 mL; 1.94 mol) was added to a suspension of 5-bromo-*N*<sup>2</sup>-[4-((*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-*N*<sup>4</sup>-(4-fluoro-phenyl)-pyrimidine-2,4-diamine (10.57 g; 0.02 mol) in methanol (675 mL), stirring under argon. After stirring at room temperature overnight, the mixture was concentrated in vacuo. The solid was triturated with diethyl ether, filtered, washed and dried under vacuum; it was then suspended in ethanol, and sodium bicarbonate (3.44 g; 0.04 mol) added to the stirred mixture. After stirring for 1.5 h the solid was filtered off, then stirred in water for 30 minutes. After filtering the solid and washing with water, ethanol and hexanes, 6.77 g (70%) of (*S*)-3-{4-[5-bromo-4-(4-fluoro-phenylamino)-pyrimidin-2-ylamino]-phenoxy}-propane-1,2-diol as a colorless solid, mp 207-210° C, was obtained. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 9.1δ (broad, exchangeable s, 1H), 8.6δ (broad, exchangeable s, 1H), 8.1δ (s, 1H), 7.6δ (m, 2H), 7.4δ (d, 2H), 7.2δ (m, 2H), 6.7δ (d, 2H), 4.9δ (broad, exchangeable s, 1H), 4.6δ (broad, exchangeable s, 1H), 3.9δ (dd, 1H), 3.8δ (m, 2H), 3.4δ (d, 2H); LCMS *m/z* 449 + 451 (*M*+*H*<sup>+</sup>), RT = 1.9 min.; Anal. Calcd. for C<sub>19</sub>H<sub>18</sub>BrFN<sub>4</sub>O<sub>3</sub>: C, 50.79; H, 4.04; N, 12.47. Found: C, 50.77; H, 3.91; N, 12.39; chiral HPLC (CHIRALPAK AD-H, 4.6 X 250 mm., 1.0 mL/min., 280 nm, hexane + 0.1% TFA/ isopropanol + 0.1% TFA gradient): RT = 12.0 min., ee >98%.

Example 13

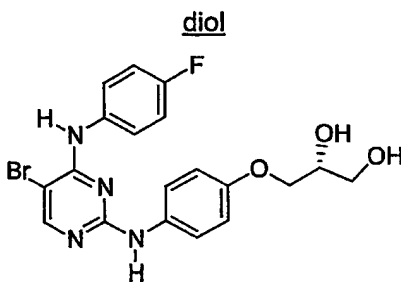
5-Bromo-*N*<sup>2</sup>-[4-((*S*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-*N*<sup>4</sup>-(4-fluoro-phenyl)-pyrimidine-2,4-diamine



A stirred suspension of 4-[5-bromo-4-(4-fluoro-phenylamino)-pyrimidin-2-ylamino]-phenol (11.14 g; 0.03 mol), toluene-4-sulfonic acid (*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester (10.2 g; 0.04 mol) and cesium carbonate (29.31 g; 0.09 mol) in anhydrous *N,N*-dimethylformamide (120 mL) was heated under argon atmosphere at 90° C for 1.5 h, then allowed to cool to room temperature. The reaction mixture was partitioned between ethyl acetate (250 mL) and brine (500 mL), the phases separated, and the aqueous phase extracted with ethyl acetate (2 X 125 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried (anhydrous sodium sulfate), then filtered through a pad of silica gel. The pad was eluted with ethyl acetate, and the filtrate concentrated in vacuo to afford crude product. Purification by column chromatography on silica gel (hexane/ dichloromethane/ ethyl acetate solvent gradient) afforded 5-bromo-*N*<sup>2</sup>-[4-((*S*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-*N*<sup>4</sup>-(4-fluoro-phenyl)-pyrimidine-2,4-diamine as a tan solid (11 g; 74.5%), mp slowly melts 95-116.5° C. <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>): 8.1δ (s, 1H), 7.5δ (m, 2H), 7.3δ (m, 2H), 7.1δ (m, 3H), 7.0δ (broad, exchangeable s, 1H), 6.8δ (m, 2H), 4.4δ (m, 1H), 4.1δ (dd, 1 H), 4.0δ (dd, 1H), 3.9δ (dd, 1 H), 3.8δ (dd, 1 H), 1.45 (d, 3H), 1.4 (d, 3H); LCMS *m/z* 489 + 491 (*M*+*H*<sup>+</sup>), RT = 2.6 min.

#### Example 14

(*R*)-3-{4-[5-Bromo-4-(4-fluoro-phenylamino)-pyrimidin-2-ylamino]-phenoxy}-propane-1,2-

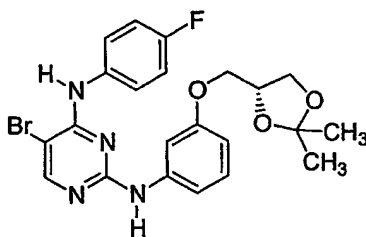


Trifluoroacetic acid (160 mL; 2.08 mol) was added to a suspension of 5-bromo-*N*<sup>2</sup>-[4-((*S*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-*N*<sup>4</sup>-(4-fluoro-phenyl)-pyrimidine-2,4-diamine (10.9 g; 0.02 mol) in methanol (640 mL), stirring under argon. After stirring at room temperature overnight, the mixture was concentrated in vacuo. The solid was triturated with diethyl ether and filtered; it was then suspended in water (250 mL), and sodium bicarbonate (3.74 g; 0.04 mol) added to the vigorously stirred mixture. After 20 minutes the solid was filtered off, washed with water, ethanol and hexanes to afford (*R*)-3-{4-[5-bromo-4-(4-fluoro-phenylamino)-pyrimidin-2-ylamino]-phenoxy}-propane-1,2-diol as 8.65 g (88%) of nearly colorless solid, mp 206.5-208.5° C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 9.1δ (broad, exchangeable s, 1H), 8.6δ (broad, exchangeable s, 1H), 8.1δ (s, 1H), 7.6δ (m, 2H), 7.4δ (d, 2H), 7.2δ (m, 2H), 6.7δ (d, 2H), 4.9δ (broad, exchangeable

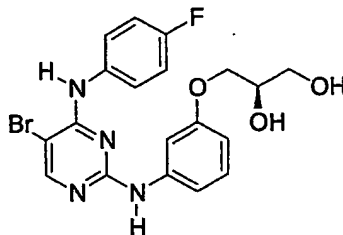
s, 1H), 4.6δ (broad, exchangeable s, 1H), 3.9δ (dd, 1H), 3.8δ (m, 2 H), 3.4δ (d, 2H); LCMS m/z 449 + 451 (M+H<sup>+</sup>), RT = 1.9 min.; Anal. Calcd. for C<sub>19</sub>H<sub>18</sub>BrFN<sub>4</sub>O<sub>3</sub>: C, 50.79; H, 4.04; N, 12.47. Found: C, 50.57; H, 4.0; N, 12.32; chiral HPLC (CHIRALPAK AD-H, 4.6 X 250 mm., 1.0 mL/min., 280 nm, hexane + 0.1% TFA/ isopropanol + 0.1% TFA gradient): RT = 14.0 min., ee >99%.

#### Example 15

#### 5-Bromo-N<sup>2</sup>-[3-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-N<sup>4</sup>-(4-fluoro-phenyl)-pyrimidine-2,4-diamine



A stirred suspension of 3-[5-bromo-4-(4-fluoro-phenylamino)-pyrimidin-2-ylamino]-phenol (14.27 g; 0.04 mol), toluene-4-sulfonic acid (S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester (21.78 g; 0.08 mol) and cesium carbonate (43.82 g; 0.13 mol) in anhydrous *N,N*-dimethylformamide (150 mL) was heated under argon atmosphere at 90° C for 1 hour, then allowed to cool to room temperature. The reaction mixture was partitioned between ethyl acetate (150 mL) and brine (450 mL), the phases separated, and the aqueous phase extracted with ethyl acetate (2 X 100 mL). The combined organic extracts were washed with water (200 mL) and brine (200 mL), dried (anhydrous sodium sulfate), then filtered through a pad of silica gel. The pad was eluted with ethyl acetate, and the filtrate concentrated in vacuo to afford crude product. Purification by column chromatography on silica gel (hexane/ dichloromethane/ ethyl acetate solvent gradient) afforded 5-bromo-N<sup>2</sup>-[3-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-N<sup>4</sup>-(4-fluoro-phenyl)-pyrimidine-2,4-diamine as a foam (13.85 g; 74.5%). <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>): 8.1δ (s, 1H), 7.5δ (m, 2H), 7.3δ (t, 2H), 7.2δ (broad, exchangeable s, 1H), 7.1δ (m, 3H), 7.0δ (m, 1H), 6.6δ (m, 1H), 4.4δ (m, 1H), 4.1δ (dd, 1 H), 4.0δ (dd, 1H), 3.9δ (dd, 1 H), 3.8δ (dd, 1 H), 1.43δ (s, 3H), 1.4δ (s, 3H); LCMS m/z 489 + 491 (M+H<sup>+</sup>), RT = 2.9 min.

Example 16(S)-3-{3-[5-Bromo-4-(4-fluoro-phenylamino)-pyrimidin-2-ylamino]-phenoxy}-propane-1,2-diol (add to table)

5 Trifluoroacetic acid (200 mL; 2.6 mol) was added to a suspension of 5-bromo-*N*<sup>2</sup>-[3-((*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-*N*<sup>4</sup>-(4-fluoro-phenyl)-pyrimidine-2,4-diamine (13.71 g; 0.03 mol) in methanol (800 mL), stirring under argon. After stirring for 2 h at room temperature, the mixture was concentrated in vacuo. The residue was

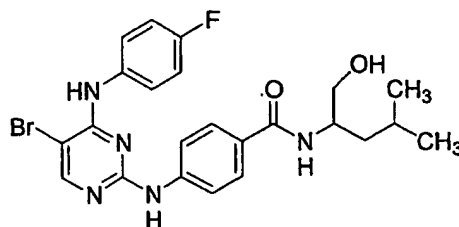
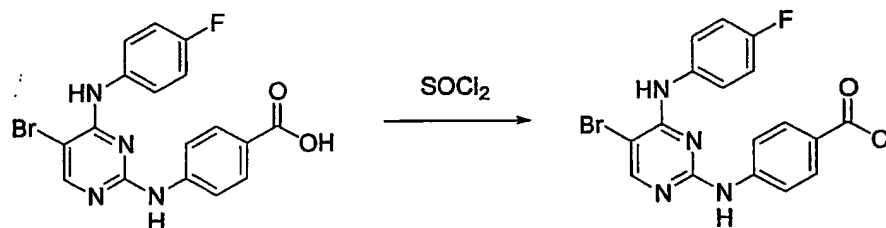
10 partitioned between water, ethanol and dichloromethane, and the phases separated; upon washing the organic phase with brine, solid formed. The solid was filtered off, then suspended in water (250 mL), and sodium bicarbonate (4.71 g; 0.06 mol) added to the vigorously stirred mixture. After stirring overnight, the solid was filtered off, washed with

15 water, ethanol and hexanes to afford 7.3 g (58%) of (S)-3-{3-[5-bromo-4-(4-fluoro-phenylamino)-pyrimidin-2-ylamino]-phenoxy}-propane-1,2-diol as a nearly colorless solid, mp 169.5-172° C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 9.2δ (exchangeable s, 1H), 8.6δ (exchangeable s, 1H), 8.2δ (s, 1H), 7.6δ (m, 2H), 7.2δ (m, 4H), 7.0δ (t, 1H), 6.5δ (m, 1H), 4.9δ (broad, exchangeable s, 1H), 4.6δ (broad, exchangeable s, 1H), 3.9δ (d, 1H), 3.7δ (m, 2H), 3.4δ (broad s, 2H); LCMS *m/z* 449 + 451 (M+H<sup>+</sup>), RT = 2.1 min.; Anal. Calcd. for C<sub>19</sub>H<sub>18</sub>BrFN<sub>4</sub>O<sub>3</sub>: C, 50.79; H, 4.04; N, 12.47. Found: C, 50.76; H, 3.91; N, 12.42; chiral

20 HPLC (CHIRALPAK AD-H, 4.6 X 250 mm., 1.5 mL/min., 280 nm, hexane + 0.1% TFA/25% methanol:isopropanol + 0.1% TFA gradient): RT = 19.9 min., ee >99%.

Example 17Methods 17a and 17bPreparation of 4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-N-[1-(hydroxymethyl)-3-methylbutyl]benzamide

5

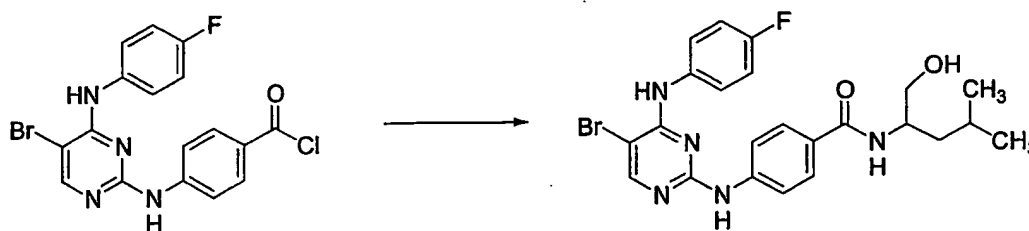
Step 1. Method 17a Preparation of 4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)benzoyl chloride

10

A mixture of the carboxylic acid (2.48mmol) was treated with 20 mL of thionyl chloride and allowed to stir at room temperature for 1 hour. The solution was then allowed to stir at 50°C for 18 h. The solution was then concentrated and the crude product was used directly in amide coupling reactions.

Step 2. Method 17b Preparation of 4-({5-bromo-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-N-[1-(hydroxymethyl)-3-methylbutyl]benzamide

15

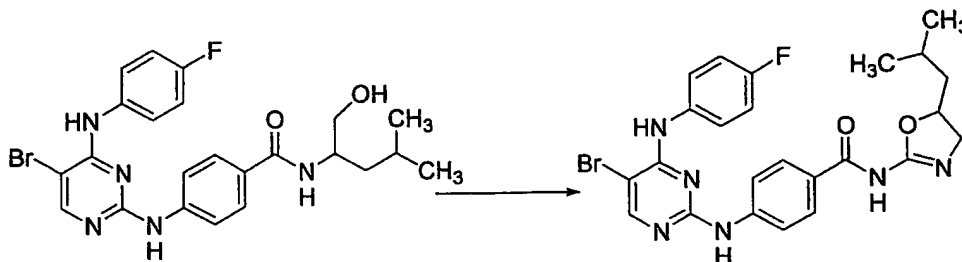


20

A solution of the acid chloride and the amine (or hydrazine) were combined, followed by the addition of pyridine and dichloromethane. The reaction was allowed to stir at rt for 18 h. The reaction was then filtered and washed with methylene chloride. The product was purified by HPLC, and was used directly in a subsequent step without purification.

Example 18Method 18

Preparation of 4-((5-bromo-4-((4-fluorophenyl)amino)-2-pyrimidinyl)amino)-N-(5-isobutyl-4,5-dihydro-1,3-oxazol-2-yl)benzamide (need table entry)



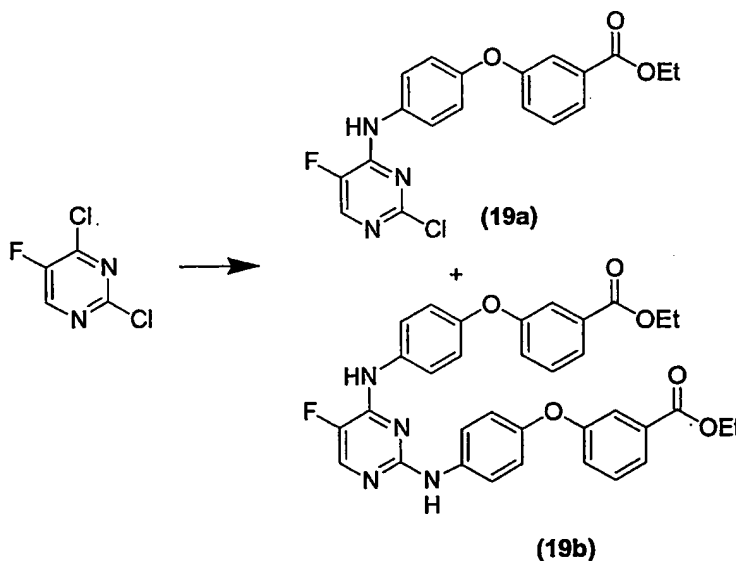
5

The amide was combined with thionyl chloride and methylene chloride. The reaction mixture was allowed to stir for 30 minutes and then warmed to room temperature. The mixture was concentrated and then dissolved in DMSO for HPLC purification.

10

Example 19Method 19

Preparation of Ethyl 3-(4-((2-chloro-5-fluoro-4-pyrimidinyl)amino)phenoxy)benzoate (19a) and Ethyl 3-(4-((2-((4-((3-ethoxycarbonyl)phenoxy)phenyl)amino)-5-fluoro-4-pyrimidinyl)amino)phenoxy)benzoate (19b)



15

A solution of 2,4-dichloro-5-fluoropyrimidine (3.24 g, 19.4 mmol) and ethyl 3-(4-aminophenoxy)benzoate (1.00 g, 3.89 mmol) in 4M HCl in dioxane (20 mL) was refluxed for 1 h. TLC analysis indicates two products. The reaction was cooled, quenched with 10% K<sub>2</sub>CO<sub>3</sub> (150 mL) and quickly extracted with EtOAc (3 X 300 mL). The organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The crude products were separated and purified by silica

20

gel chromatography (ethyl acetate/hexane) to give ethyl 3-{4-[(2-chloro-5-fluoro-4-pyrimidinyl)amino]phenoxy}-benzoate (19a) as a tan solid in 40% yield (0.630 g, 1.63 mmol) and ethyl 3-(4-{[2-({4-[3(ethoxycarbonyl)phenoxy]phenyl}amino)-5-fluoro-4-pyrimidinyl]-amino}phenoxy)benzoate (19b) as a tan solid in 20% yield (0.470 g, 0.772 mmol).

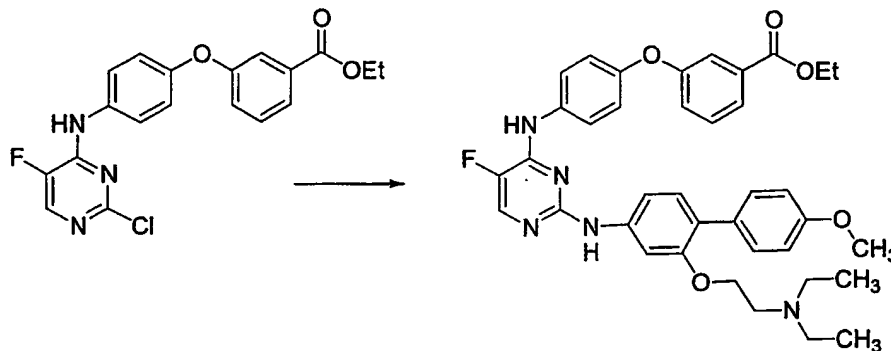
5 Ethyl 3-{4-[(2-chloro-5-fluoro-4-pyrimidinyl)amino]phenoxy}-benzoate (19a): TLC:  $R_f$  = 0.36 (30% EtOAc/hexane; LC-MS (ESI):  $[M+H]^+$  388.2 @ RT 3.41 min.;  $^1H$  NMR (DMSO)  $\delta$  10.03 (1H, s), 8.30 (1H, d,  $J$  = 3.3 Hz), 7.70 (3H, m), 7.53 (1H, t,  $J$  = 8.1 Hz), 7.44 (1H, s), 7.30 (1H, dd,  $J$  = 2.7, 8.4 Hz), 7.10 (2H, d,  $J$  = 8.7 Hz), 4.28 (2H, quart,  $J$  = 6.9 Hz), 1.27 (3H, t,  $J$  = 6.9 Hz).

10 Ethyl 3-(4-{[2-({4-[3(ethoxycarbonyl)phenoxy]phenyl}amino)-5-fluoro-4-pyrimidinyl]-amino}phenoxy)benzoate(19b): TLC:  $R_f$  = 0.21 (30% EtOAc/hexane; LC-MS (ESI):  $[M+H]^+$  609.5 @ RT 3.21 min.;  $^1H$  NMR (DMSO)  $\delta$  9.44 (1H, s), 9.28 (1H, s), 8.10 (1H, d,  $J$  = 3.9 Hz), 7.80 (2H, d,  $J$  = 9 Hz), 7.70 (2H, d,  $J$  = 9 Hz), 7.59 (2H, t,  $J$  = 7.8 Hz), 7.43 (2H, t,  $J$  = 7.8 Hz), 7.36 (2H, m), 7.21 (2H, m), 7.03 (2H, d,  $J$  = 9 Hz), 6.93 (2H, d,  $J$  = 9 Hz), 4.23 (4H, quart,  $J$  = 7.2 Hz), 1.24 (6H, t,  $J$  = 6.6 Hz).

#### Example 20

#### Method 20

#### Preparation of ethyl 3-(4-{[2-({2-[2-(diethylamino)ethoxy]-4'-methoxy-1,1'-biphenyl-4-yl}amino)-5-fluoro-4-pyrimidinyl]amino}phenoxy)benzoate



20

To a solution of ethyl 3-{4-[(2-chloro-5-fluoro-4-pyrimidinyl)amino]phenoxy} benzoate (51 mg, 0.13 mmol) and 2-[2-(diethylamino)ethoxy]-4'-methoxy-1,1'-biphenyl-4-amine (33 mg, 0.10 mmol) in  $CH_2Cl_2$  (5 mL) was added 4M HCl in dioxane (3 mL) and the solution heated in an open vial at 110 °C. The reaction was slowly concentrated over 4 h to a gum as the solvent was boiled off. The reaction was cooled and the gum was dissolved in EtOH (10 mL) and quenched with 10%  $K_2CO_3$  (50 mL). This was quickly extracted with EtOAc (2 X 150 mL), and the organic layers dried ( $Na_2SO_4$ ) and concentrated *in vacuo* to give a crude amber oil. This was purified by reverse-phase prep-HPLC (RT = 6.28 min), and the TFA salt of the isolated product dissolved in  $CH_2Cl_2$

25

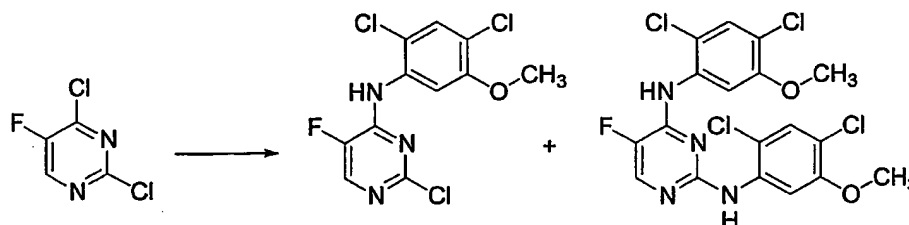
and free based by washing with 5% K<sub>2</sub>CO<sub>3</sub>. The organic layer was concentrated *in vacuo* to give the product as a hygroscopic brown solid in 54% yield (38 mg, 0.057 mmol).

TLC: *R<sub>f</sub>* = 0.34 (50/45/5 CH<sub>3</sub>CN/MeOH/H<sub>2</sub>O); LC-MS (ESI): [M+H]<sup>+</sup> 666.6 @ RT 2.60 min.; <sup>1</sup>H NMR (DMSO) δ 7.93 (1H, d, *J* = 3.0 Hz), 7.74 (3H, m), 7.59 (1H, d, *J* = 1.2 Hz), 7.41 (1H, t, *J* = 7.8), 7.31 (3H, m), 7.23 (2H, m), 7.07 (1H, d, *J* = 8.4 Hz), 7.01 (2H, d, *J* = 8.7 Hz), 6.87 (2H, d, *J* = 8.4 Hz), 4.29 (2H, quart, *J* = 6.9 Hz), 3.93 (2H, t, *J* = 6.0 Hz), 3.81 (3H, s), 2.80 (2H, t, *J* = 5.7 Hz), 2.52 (4H, quart, *J* = 6.9 Hz), 1.32 (3H, t, *J* = 6.9 Hz), 0.94 (6H, t, *J* = 7.5 Hz).

### Example 21

#### Method 21

Preparation of 2-chloro-*N*-(2,4-dichloro-5-methoxyphenyl)-5-fluoro-4-pyrimidinamine and *N*-(2,4-dichloro-5-methoxyphenyl)-*N*-(2-[(2,4-dichloro-5-methoxyphenyl)amino]-5-fluoro-4-pyrimidinyl)amine



A homogenous mixture of 2,4-dichloro-5-fluoropyrimidine 1 (2.61 g, 15.5 mmol) and 2,4-dichloro-5-methoxyaniline 7 (1.00 g, 5.16 mmol) and concentrated HCl (1.72 mL, 20.6 mmol) was heated at 110 °C for 2.5 h. The reaction was quenched with saturated K<sub>2</sub>CO<sub>3</sub> (150 mL) and extracted with EtOAc (3 X 300 mL). The organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The crude product was suspended in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and the white solid hydrolysis by-product filtered off. The filtrate was purified by silica gel chromatography (EtOAc/hexane), and the semi-pure residue was suspended in EtOAc. *N*-(2,4-dichloro-5-methoxyphenyl)-*N*-(2-[(2,4-dichloro-5-methoxyphenyl)amino]-5-fluoro-4-pyrimidinyl)amine was isolated as an insoluble white solid in 5% yield (55 mg, 0.12 mmol). The filtrate was re-purified by silica gel chromatography (MeOH/ CH<sub>2</sub>Cl<sub>2</sub>) to give 2-chloro-*N*-(2,4-dichloro-5-methoxyphenyl)-5-fluoro-4-pyrimidinamine as a white solid in 33% yield (566 mg, 1.72 mmol).

2-Chloro-*N*-(2,4-dichloro-5-methoxyphenyl)-5-fluoro-4-pyrimidinamine: TLC: *R<sub>f</sub>* = 0.34 (20% EtOAc/hexane; LC-MS (ESI): [M+H]<sup>+</sup> 322.1 @ RT 3.09 min.; <sup>1</sup>H NMR (DMSO) δ 8.46 (1H, s), 8.18 (1H, d, *J* = 2.4 Hz), 7.56 (1H, b s), 7.43 (1H, s), 3.98 (3H, s).

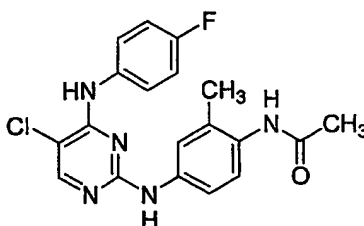
*N*-(2,4-dichloro-5-methoxyphenyl)-*N*-(2-[(2,4-dichloro-5-methoxyphenyl)amino]-5-fluoro-4-pyrimidinyl)amine: TLC: *R<sub>f</sub>* = 0.34 (20% EtOAc/hexane; LC-MS (ESI): [M+H]<sup>+</sup> 479.2 @ RT

3.87 min.;  $^1\text{H}$  NMR (DMSO)  $\delta$  8.23 (1H, s), 8.21 (1H, s), 8.10 (1H, d,  $J = 2.7$  Hz), 7.43 (1H, s), 7.37 (1H, s), 7.34 (2H, b s), 3.79 (3H, s), 3.75 (3H, s).

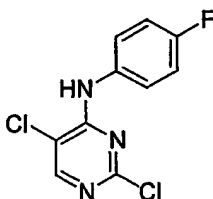
### Example 22

#### Method 22

#### 5 Preparation of *N*-[4-({5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]acetamide



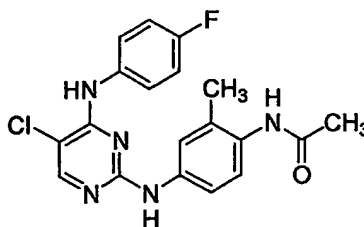
#### Step 1: Preparation of 2,5-dichloro-*N*-(4-fluorophenyl)-4-pyrimidinamine



10 To a suspension 2,4,5-trichloropyrimidine (3.00 g, 16.4 mmol) and  $\text{Na}_2\text{CO}_3$  (6.93 g, 65.4 mmol) in EtOH (200 mL) was added 4-fluoroaniline (2.18 g, 19.6 mmol) dropwise. The reaction mixture was stirred at rt overnight. TLC and LCMS showed the reaction was complete. The mixture was filtered and the solvent evaporated *in vacuo*. The residue was dissolved in DCM and washed with brine. The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and

15 concentrated to give 3.89 g of a white solid (92%).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  8.20 (s, 1H), 7.59-7.55 (q, 2H), 7.14-7.09 (t, 2H); LCMS RT = 2.79 min;  $[\text{M}+\text{H}]^+$  258.

#### Step 2: Preparation of *N*-[4-({5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]acetamide



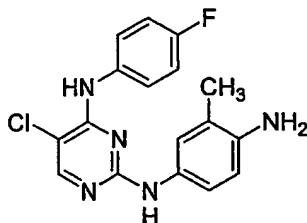
20 A suspension of 2,5-dichloro-*N*-(4-fluorophenyl)-4-pyrimidinamine (121 mg, 0.47 mmol) and 1-(4-amino-2-methyl)phenylacetamide (93 mg, 0.56 mmol) in *n*-BuOH (1 mL) was stirred at 110 °C for 24 h. The resulting precipitate was filtered and washed with EtOH followed by  $\text{Et}_2\text{O}$  to give 179 mg of a yellow solid (98%).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.07

(s, 1H), 7.55-7.51 (q, 2H), 7.32-7.30 (d, 1H), 7.25 (d, 1H), 7.18-7.13 (m, 3H), 2.18 (s, 6H); LCMS RT = 2.56 min;  $[M+H]^+$  386.

### Example 23

#### Method 23

#### 5 Preparation of *N*-(4-amino-3-methylphenyl)-*N*-(5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)amine

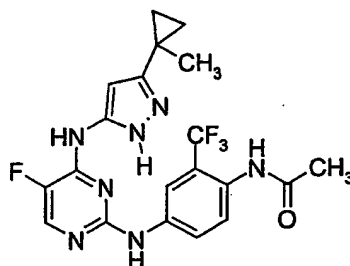


To a suspension of *N*-(4-[(5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)amino]-2-methylphenyl)-acetamide (125 mg, 0.30 mmol) in *n*-BuOH (10mL) was added conc. HCl (2mL) dropwise. The mixture was stirred at 100 °C for 24 h. TLC and LCMS showed the reaction was complete. The reaction solution was evaporated *in vacuo*, and the residue was dissolved in DCM (210 mL). This was washed with 1M NaOH (10 mL) then brine (10 mL). The organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to furnish 92 mg of a white powder (89%).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.90 (s, 1H), 7.61-7.58 (q, 2H), 7.12-7.11 (d, 1H), 7.05-7.00 (m, 3H), 6.66-6.64 (d, 1H), 2.11 (s, 3H); LCMS RT=0.32 min;  $[M+H]^+$  344.

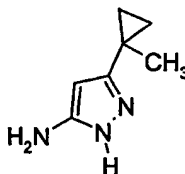
### Example 24

#### Method 24

#### 20 Preparation of *N*-(4-(5-fluoro-4-[5-(1-methylcyclopropyl)-2H-pyrazol-3-ylamino]-pyrimidin-2-ylamino)-2-methylphenyl)-acetamide

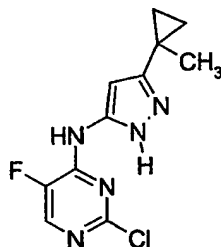


#### Step 1: Preparation of 5-(1-methylcyclopropyl)-2H-pyrazol-3-ylamine



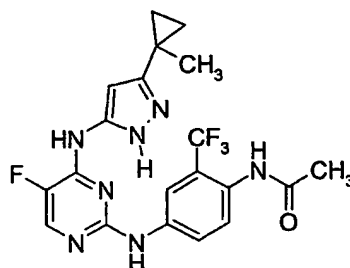
A suspension of NaH (60% dispersion in mineral oil) (4.20 g, 175 mmol) in anhydrous THF (100 mL) was treated with anhydrous CH<sub>3</sub>CN (9.14 mL, 175 mmol), and the suspension was stirred at ambient temperature for 10 min. To this was added 1-methylcyclopropane-1-carboxylic acid methyl ester (9.70 g, 83.3 mmol), and the reaction was heated to reflux for 24 h. The reaction was quenched by addition of abs EtOH (75 mL), and the slurry concentrated to a white solid. This was dissolved in H<sub>2</sub>O (100 mL) and further quenched with conc. HCl (20 mL) at 5 °C to a final pH of 2. This was extracted with EtOAc (3 X 250 mL), the combined organic layers dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent removed *in vacuo* to give the crude  $\alpha$ -cyanoketone intermediate as an amber oil. This was dissolved in abs EtOH (75 mL), hydrazine hydrate (8.62 g, 172 mmol) was added, and the solution was heated to reflux for 24 h. The reaction was concentrated *in vacuo* to an oil, which was purified by silica gel chromatography (5% MeOH/DCM) to give the product as an orange oil in 54% yield (7.11 g, 51.8 mmol). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  5.34 (s, 1H), 1.38 (s, 3H), 0.84 and 0.73 (2 m, 4H); LCMS RT = 0.77 min; [M+H]<sup>+</sup> = 138.1.

Step 2: Preparation of (2-chloro-5-fluoropyrimidin-4-yl)-[5-(1-methylcyclopropyl)-2H-pyrazol-3-yl]-amine



A solution of 2,4-dichloro-5-fluoropyrimidine (1.11 g, 6.58 mmol), 5-(1-methylcyclopropyl)-2H-pyrazol-3-ylamine (1.00 g, 6.58 mmol), and KOAc (0.780 g, 7.90 mmol) in H<sub>2</sub>O (10 mL) and THF (20 mL) was heated to 45 °C for 24 h. The reaction was quenched with sat. NaHCO<sub>3</sub> (100 mL) and extracted with EtOAc (2 X 250 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to a white solid. The crude material was purified by silica gel chromatography (50% EtOAc/Hex) to give the product as a white solid in 93% yield (1.69 g, 6.31 mmol). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  12.17 (b s, 1H), 10.35 (s, 1H), 8.22 (d, J = 3.6 Hz, 1H), 6.28 (s, 1H), 1.37 (s, 3H), 0.87 and 0.75 (2 m, 4H); LCMS RT = 2.32 min; [M+H]<sup>+</sup> = 268.3.

Step 3. Preparation of *N*-(4-{5-fluoro-4-[5-(1-methylcyclopropyl)-2*H*-pyrazol-3-ylamino]-pyrimidin-2-ylamino}-2-methylphenyl)-acetamide

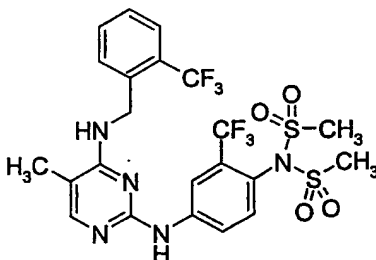


The compound was prepared by the method described for Example 22, step 2, using the product of Example 24, step 2, and *N*-(4-amino-2-methylphenyl)-acetamide as starting materials. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.39 (b s, 1H), 10.04 (s, 1H), 9.43 (s, 1H), 8.19 (d, *J* = 3.9 Hz, 1H), 7.96 (m, 2H), 7.34 (d, *J* = 8.7 Hz, 1H), 6.18 (s, 1H), 2.10 (s, 3H), 1.37 (s, 3H), 0.90 and 0.75 (2 m, 4H); LCMS RT = 2.11 min; [M+H]<sup>+</sup> = 450.3.

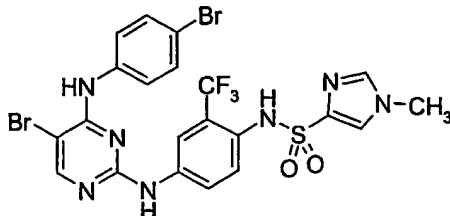
Example 25

Method 25

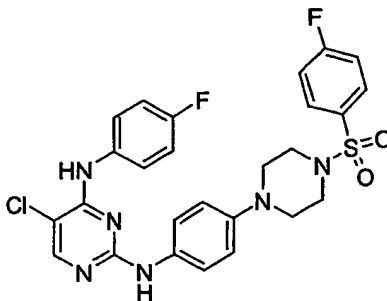
Preparation of *N*-(methanesulfonyl)-*N*-[4-[(5-methyl-4-[[2-(trifluoromethyl)benzyl]amino]-2-pyrimidinyl)amino]-2-(trifluoromethyl)phenyl]methanesulfonamide



To a mixture of *N*-[4-amino-3-(trifluoromethyl)phenyl]-*N*-(5-methyl-4-[[2-(trifluoromethyl)benzyl]amino]-2-pyrimidinyl)amine (200 mg, 0.45 mmol) and Et<sub>3</sub>N (44 mg, 1.36 mmol) in DCM (5 mL) was added methanesulfonyl chloride (62 mg, 0.54 mmol) at 0 °C. The solution was stirred at room temperature for 4 h then quenched with water. DCM was added (25 mL) and the organic layer was washed with brine. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The crude material was recrystallized from EtOAc/Hex (1:1) to give the product as white solid in 56% yield (152 mg). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.54 (s, 1H); 8.26 (d, 1H); 7.84 (m, 2H); 7.75 (d, 1H); 7.61 (t, 1H); 7.45 (m, 3H); 7.34 (d, 1H); 4.87 (d, 2H); 3.48 (s, 6H); 2.06 (s, 3H); LCMS RT = 2.56 min; [M+H]<sup>+</sup> 598.0

Example 26Method 26Preparation of *N*-{5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}-*N*-(4-{4-[(4-fluorophenyl)sulfonyl]-1-piperazinyl}phenyl)amine

To a solution of *N*-(4-amino-3-trifluoromethylphenyl)-*N*-[5-bromo-4-[(4-bromophenyl)amino]-2-pyrimidinyl]amine (8.00 g, 15.9 mmol) and 4-(dimethylamino)pyridine (1.94 g, 15.9 mmol) in pyridine (250 mL) at 0 °C was added 1-methylimidazole-4-sulphonyl chloride (4.88 g, 27.0 mmol) in several portions. The reaction was stirred at rt for 48 h then quenched with MeOH. The reaction was concentrated and MeOH (100 mL) was added to the resulting residue. The resulting white precipitate was filtered and washed with Hex/EtOAc (1:1) followed by MeOH to obtain the desired product in 84% yield (8.77 g). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 9.69 (s, 1H), 9.47 (s, 1H), 8.80 (s, 1H), 8.29 (s, 1H), 7.90-7.88 (dd, 2H), 7.82-7.78 (dd, 1H), 7.69 (d, 1H), 7.57 (d, 2H), 7.48 (d, 2H), 7.11 (d, 1H), 3.72 (s, 3H); LCMS RT = 2.90 min; [M+H]<sup>+</sup> = 646.0; Anal. Calcd. for C<sub>21</sub>H<sub>16</sub>Br<sub>2</sub>F<sub>3</sub>N<sub>7</sub>O<sub>2</sub>S: C, 38.97; H, 2.49; N, 15.15. Found: C, 38.97; H, 2.49; N, 15.11.

Example 27Method 27Preparation of *N*-{5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl}-*N*-(4-{4-[(4-fluorophenyl)sulfonyl]-1-piperazinyl}phenyl)amine

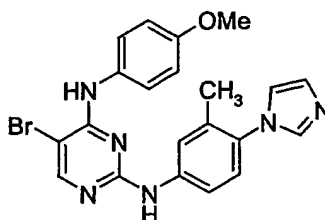
To a solution of *N*-(5-chloro-4-[(4-fluorophenyl)amino]-2-pyrimidinyl)-*N*-(4-(1-piperazinyl)phenyl)amine (100 mg, 0.25 mmol) in DCM (2.0 mL) was added Et<sub>3</sub>N (0.10 mL, 0.75 mmol). After 5 min, 4-fluorobenzenesulfonyl chloride (146 mg, 0.75 mmol) was added, and the mixture stirred at rt for 24 h. The reaction was diluted with EtOAc (75 mL)

and washed with sat.  $\text{NaHCO}_3$  (75 mL) and brine (75 mL). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The crude product was rinsed with MeOH (5 mL) followed by DCM (5 mL) to afford pure product in 29% yield (40 mg).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  9.10 (s, 1H), 8.81 (s, 1H), 8.06 (s, 1H), 7.85 (t, 2H), 7.65 (t, 2H), 7.54 (t, 2H), 7.39 (d, 2H), 7.16 (t, 2H), 6.75 (d, 2H), 3.09 (b, 4H), 3.02 (b, 4H); LCMS RT = 2.78 min;  $[\text{M}+\text{H}]^+$  557.2.

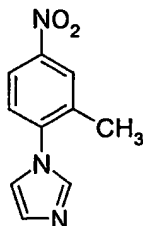
### Example 28

#### Method 28

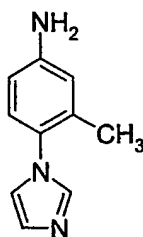
#### Preparation of {5-bromo-4-[(4-methoxyphenyl)amino]pyrimidin-2-yl}{4-imidazolyl-3-methylphenyl}amine



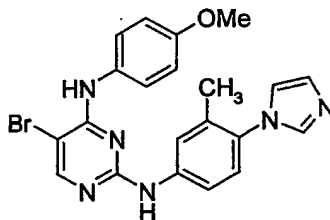
#### Step 1: Preparation of 1-(2-Methyl-4-nitro-phenyl)-1H-imidazole



To a solution of 2-fluoro-5-nitrotoluene (5.00 g, 32.2 mmol) and 1H-imidazole (2.19 g, 32.2 mmol) in DMF (75 mL) was added  $\text{K}_2\text{CO}_3$  (6.68 g, 48.3 mmol) in several portions. The reaction was heated to 80 °C overnight. The solvent was removed under vacuum. The residue was diluted with EtOAc (250 mL). The solution was washed with brine (75 mL X 5). The solution was concentrated in vacuo. The residue was filtered and washed with hexanes (20 mL X 3). The filter cake was then dried under vacuum to afford desired product as a yellow solid in 68% yield (4.43 g).  $^1\text{H}$ -NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  8.28 (d, 1H), 8.15 (d, 1H), 7.89 (s, 1H), 7.53 (d, 1H), 7.37 (s, 1H), 7.16 (s, 1H), 2.31 (s, 3H); LCMS RT = 0.84 min;  $[\text{M}+\text{H}]^+$  = 204.1.

Step 2: Preparation of 4-Imidazole-1-yl-3-methyl-phenylamine

A solution of 1-(2-methyl-4-nitro-phenyl)-1*H*-imidazole (3.43 g, 16.9 mmol) in EtOH (380 mL) was added to a flask containing 10% palladium on carbon (360 mg). The reaction vessel was fitted with a balloon adapter and charged with hydrogen and evacuated three times until the reaction was under a H<sub>2</sub> atmosphere. The reaction was allowed to stir overnight and then purged with Ar and evacuated three times until an Ar atmosphere had been achieved. The reaction solution was filtered through a pad of Celite® and washed with copious amounts of EtOH. The filtrate was concentrated under vacuum to afford desired product in 94% yield (2.90 g) as a yellow solid. <sup>1</sup>H-NMR (CD<sub>3</sub>OD): δ 7.60 (s, 1H), 7.09 (s, 1H), 7.04 (s, 1H), 6.90 (d, 1H), 6.65 (d, 1H), 6.52-6.58 (dd, 1H), 1.97 (s, 3H); LCMS RT = 0.71 min; [M+H]<sup>+</sup> = 174.2.

Step 3: Preparation of {5-bromo-4-[(4-methoxyphenyl)amino]pyrimidin-2-yl}(4-imidazolyl-3-methylphenyl)amine

The compound was prepared by the method described for Example 22, step 2, step 2, using the product of Example 29, step 2 and 2,5-dichloro-*N*-(4-methoxyphenyl)-4-pyrimidinamine as starting materials. <sup>1</sup>H NMR (CD<sub>3</sub>OD) 8.06 (s, 1H), 7.66 (s, 1H), 7.55 (s, 1H), 7.38-7.32 (m, 3H), 7.15(s, 1H) 7.08 (s, 1H), 6.99 (d, 1H), 6.94 (s, 1H), 6.91 (s, 1H), 3.76 (s, 3H), 1.93 (s, 3H); LCMS RT = 1.91 min; [M+H]<sup>+</sup> = 451.3.

The compounds of Table I were made using a combination of the above described procedures, and the appropriate starting materials. The actual sequence of steps used to prepare each compound are indicated in Table I in the column labeled "method" for that compound, in which the entries refer to the specific synthetic methods described above. Thus the preparation of each compound is achieved by carrying out each synthetic step in the order listed, using the appropriately substituted starting materials, as would be obvious to one skilled in the art.

Variations of the compounds of the invention can be readily prepared using the processes described above, or by other standard chemical processes known in the art, by employing appropriate starting materials that are readily available and/or are already described herein, as would be known by one skilled in the art.

5           Generally, a desired salt of a compound of this invention can be prepared in situ during the final isolation and purification of a compound by means well known in the art. For example, a desired salt can be prepared by separately reacting the purified compound in its free base or free acid form with a suitable organic or inorganic acid, or  
10           suitable organic or inorganic base, respectively, and isolating the salt thus formed. In the case of basic compounds, for example, the free base is treated with anhydrous HCl in a suitable solvent such as THF, and the salt isolated as a hydrochloride salt. In the case of  
15           acidic compounds, the salts may be obtained, for example, by treatment of the free acid with anhydrous ammonia in a suitable solvent such as ether and subsequent isolation of the ammonium salt. These methods are conventional and would be readily apparent to  
one skilled in the art.

The purification of isomers of a compound of this invention, and the separation of said isomeric mixtures can be accomplished by standard techniques known in the art.

#### Compositions of the compounds of this invention

20           The compounds of this invention can be utilized to achieve the desired pharmacological effect by administration to a patient in need thereof in an appropriately formulated pharmaceutical composition. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment (including prophylactic treatment) for the particular condition or disease.

25           Therefore, another embodiment of the present invention includes pharmaceutical compositions that are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound, or salt or ester thereof, of the present invention.

30           A pharmaceutically acceptable carrier is any carrier that is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of compound is that amount which produces a result or exerts an influence on the particular condition being treated.

35           The compounds of the present invention can be administered with pharmaceutically-acceptable carriers well known in the art using any effective

conventional dosage unit forms, including immediate, slow and timed release preparations, orally, parenterally, topically, nasally, ophthalmically, otically, sublingually, rectally, vaginally, and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule which can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatin, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, coloring agents, and flavoring agents such as peppermint, oil of wintergreen, or cherry flavoring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those sweetening, flavoring and coloring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such

as soy bean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

5           Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or *n*-propyl *p*-hydroxybenzoate; one  
10 or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

          Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavoring  
15 and coloring agents.

          The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids  
20 such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a  
25 pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

          Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil,  
30 soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides,  
35 alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and

sulfosuccinates; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

5           The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of  
10           surfactant in such formulation ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

          Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high  
15           molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

          The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example,  
20           sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example,  
25           heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

          The sterile injectable preparation may also be a sterile injectable solution or  
30           suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty  
35           acids such as oleic acid can be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such material are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Controlled release formulations for parenteral administration include liposomal, polymeric microsphere and polymeric gel formulations which are known in the art.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized. Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al*, "Compendium of Excipients for Parenteral Formulations" *PDA Journal of Pharmaceutical Science & Technology* **1998**, 52(5), 238-311; Strickley, R.G. "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" *PDA Journal of Pharmaceutical Science & Technology* **1999**, 53(6), 324-349; and Nema, S. *et al*, "Excipients and Their Use in Injectable Products" *PDA Journal of Pharmaceutical Science & Technology* **1997**, 51(4), 166-171.

Commonly used pharmaceutical ingredients which can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, triethylamine);

adsorbents (examples include but are not limited to powdered cellulose and activated charcoal);

aerosol propellants (examples include but are not limited to carbon dioxide,  $\text{CCl}_2\text{F}_2$ ,  $\text{F}_2\text{CIC-CClF}_2$  and  $\text{CClF}_3$ );

air displacement agents (examples include but are not limited to nitrogen and argon);

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);

antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite);

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers);

buffering agents (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate);

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection);

chelating agents (examples include but are not limited to edetate disodium and edetic acid);

colorants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);

clarifying agents (examples include but are not limited to bentonite);

emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate);

5 encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate);

flavorants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);

humectants (examples include but are not limited to glycerol, propylene glycol and sorbitol);

10 levigating agents (examples include but are not limited to mineral oil and glycerin);  
oils (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);

15 penetration enhancers (transdermal delivery) (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono- or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas);

20 plasticizers (examples include but are not limited to diethyl phthalate and glycerol);

solvents (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);

25 stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);

suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures);

30 surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate);

suspending agents (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc);

5        tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch);

10       tablet and capsule diluents (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);

15       tablet coating agents (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac);

tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate);

20       tablet disintegrants (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch);

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc);

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);

25       tablet/capsule opaquants (examples include but are not limited to titanium dioxide);

tablet polishing agents (examples include but are not limited to caruba wax and white wax);

30       thickening agents (examples include but are not limited to beeswax, cetyl alcohol and paraffin);

tonicity agents (examples include but are not limited to dextrose and sodium chloride);

35       viscosity increasing agents (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth); and

wetting agents (examples include but are not limited to heptadecaethylene

oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

It is believed that one skilled in the art, utilizing the preceding information, can utilize the present invention to its fullest extent. Nevertheless, the following are examples of pharmaceutical formulations that can be used in the method of the present invention. They are for illustrative purposes only, and are not to be construed as limiting the invention in any way.

Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile Injectable Solution

A suitable amount of pure active ingredient is dissolved in sterile, injectable water to a desired concentration, for example from about 1.0 mg/ml to about 50.0 mg/ml. U.S.P. grade sodium chloride crystals (NaCl) is added to the solution such that the final concentration of NaCl is 0.9% by weight of water. The pH of the solution is adjusted to range between approximately pH 2.0 and pH 6.0 by the addition of pure (99.999% purity) hydrochloric acid. The solution is sterilized via filtration through a sterile 0.22 micron filter. The sterile solution is stored in sealed sterile vials wherein each vial contains the desired dosage unit of active ingredient per ml of injection solution.

Sterile Injectable Solution

U.S.P. grade sodium chloride (NaCl) is dissolved in sterile, injectable water to a final concentration of 0.9% NaCl by weight of water. An amount of pure (99.999% purity) hydrochloric acid is added to the NaCl solution to obtain a final pH in the range of approximately pH2.0 to pH6.0. An amount of U.S.P. grade potassium chloride crystals (KCL) is dissolved in the solution such that the final concentration of KCl is 0.1% by weight. From 0.5 part to about thirty parts by weight of active ingredient (depending on the desired end dosage unit) is added to the solution and is completely dissolved by agitation. The pH of the solution is adjusted again to between pH2.0 and pH6.0 using pure hydrochloric acid. The solution is sterilized via filtration through a sterile 0.22 micron filter and stored in sealed sterile injection vials, each containing approximately 0.5 mg to approximately 30 mg active ingredient, depending on the final dosage unit desired in the sterile injection solution.

Sterile IV Solution:

A 5 mg/ml solution of the desired compound of this invention is made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for

administration to 1 – 2 mg/ml with sterile 5% dextrose and is administered as an IV infusion over 60 minutes.

Lyophilized powder for IV administration:

5 A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a lyophilized powder, (ii) 32- 327 mg/mL sodium citrate, and (iii) 300 – 3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or dextrose 5% to a concentration of 10 to 20 mg/mL, which is further diluted with saline or dextrose 5% to 0.2 – 0.4 mg/mL, and is administered either IV bolus  
10 or by IV infusion over 15 – 60 min.

Intramuscular suspension: The following solution or suspension can be prepared, for intramuscular injection:

50 mg/mL of the desired, water-insoluble compound of this invention  
5 mg/mL sodium carboxymethylcellulose  
15 4 mg/mL TWEEN 80  
9 mg/mL sodium chloride  
9 mg/mL benzyl alcohol

Hard Shell Capsules: A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active  
20 ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft Gelatin Capsules: A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be  
25 dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

Tablets: A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg. of starch, and  
30 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a  
35 liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction

techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

5     Method of treating pharmacological disorders

          The present invention also relates to a method of using the compounds or compositions described herein for the treatment or prevention of, or in the manufacture of a medicament for treating or preventing, mammalian hyper-proliferative disorders. This method comprises administering to a mammalian patient, including a human, in need  
10    thereof, an amount of a compound, a pharmaceutically acceptable salt thereof, or a composition of this invention that is effective to treat or prevent the disorder.

          The present invention also relates to a method for using the compounds and compositions of this invention as prophylactic or chemopreventive agents for prevention of the mammalian hyper-proliferative disorders described herein. This method comprises  
15    administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt thereof, which is effective to delay or diminish the onset of the disorder.

          The present compounds and compositions exhibit anti-proliferative activity and are thus useful to treat the disorders that are described below and/or otherwise known in the art. Hyper-proliferative disorders include diseases or conditions whose progression  
20    proceeds, at least in part, via proliferation.

          Hyper-proliferative disorders include but are not limited to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases.  
25    Those disorders also include lymphomas, sarcomas, and leukemias.

          Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

          Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.  
30    

          Examples of brain cancers include, but are not limited to brain stem and hypophthalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

35    Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not

limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

5 Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

10 Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

15 Head-and-neck cancers include, but are not limited to laryngeal / hypopharyngeal / nasopharyngeal / oropharyngeal cancer, and lip and oral cavity cancer.

Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

20 Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

25 These disorders have been well characterized in humans, and also exist with a similar etiology in other mammals which can also be treated by the administration of the compounds and/or pharmaceutical compositions of the present invention.

The utility of the compounds of the present invention can be illustrated, for example, by their activity *in vitro* in the *in vitro* tumor cell proliferation assay described below. The link between activity in tumor cell proliferation assays *in vitro* and anti-tumor activity in the clinical setting has been very well established in the art. For example, the therapeutic utility of taxol (Silvestrini et al. *Stem Cells* **1993**, 11(6), 528-35), taxotere (Bissery et al. *Anti Cancer Drugs* **1995**, 6(3), 339), and topoisomerase inhibitors (Edelman et al. *Cancer Chemother. Pharmacol.* **1996**, 37(5), 385-93) were demonstrated  
35 with the use of *in vitro* tumor proliferation assays.

The following assays are two methods by which compound activity relating to treatment of the disorders identified herein can be determined.

#### Cellular Proliferation Assay (CTG) Protocol

5 HCT-116 cells are seeded onto a 96-well culture plate at a density of 3000 cells per well in 100  $\mu$ L DMEM medium supplemented with 10% Fetal Calf Serum and incubated overnight at 37°C in 5% CO<sub>2</sub> in a humidified incubator. T<sub>0</sub> CTG measurements are taken as described below. Cells are then treated with test compounds serially diluted at 10, 3.3, 1.1, 0.33, 0.11, and 0.033  $\mu$ M and incubated for 3 days at 37°C in 5% CO<sub>2</sub> in a  
10 humidified incubator. Final concentration of DMSO in each well is 0.1%. Following three days of incubation, 100 microliters of substrate/buffer mixture of CTG (Promega Cell Titer Glo Luminescent<sup>®</sup> assay kit) are added to each well and incubated at room temperature for 30 minutes. Plates are then read in a luminometer to measure the amount of ATP present in the cell lysates, which corresponds to the number of viable cells. Values read  
15 at the time of compound administration to cells are subtracted as Day 0. For determination of IC<sub>50</sub>'s, a linear regression analysis are used to determine drug concentration which results in a 50% inhibition of cell proliferation. Percent inhibition is calculated as follows: % inhibition =  $1 - (T_{72\text{test}} - T_0) / (T_{72\text{ctrl}} - T_0) \times 100$ , where  
T<sub>72test</sub> = Value read in the presence of test compound at T = 72h  
20 T<sub>72ctrl</sub> = Value read in the absence of test compound at T = 72h  
T<sub>0</sub> = Value read in the absence of test compound at T = 0h

This assay may also be run using HT1080 or DLD-1 cell lines following the same procedure.

In vivo assay: Groups of female Ncr nude mice [Taconic Laboratories, NY] were  
25 inoculated with 3x10<sup>6</sup> cells of HCT-116, a CRC xenograft on day 0. When tumors reached a 75 to 150 mm<sup>3</sup> in size (typically 6-8 days), animals were administered compounds of interest *p.o.* in a Cremaphor (12.5%; Sigma Aldrich, St. Louis, MO): Ethanol (12.5%): Saline (75%) vehicle for 14 days. The treatment volumes were 0.1mL-test article/10g body weight. A group of 10 untreated animals was included to assess tumor response to  
30 test article vehicles. During the course of the study the animals tumor growth measurements and body weights were determined twice a week. All animals were observed for clinical signs daily and after compound administration. Tumor volume was calculated using the ellipsoid formula:

$$(D \times (d^2))/2$$

35 where,

D = diameter of the tumor at major axis

d = diameter of the tumor at minor axis

Use of compounds of this invention in the assays described above demonstrate inhibition of cell proliferation.

Based upon the above and other standard laboratory techniques known to  
5 evaluate compounds useful for the prevention and/or treatment of the diseases or  
disorders described above by standard toxicity tests and by standard pharmacological  
assays for the determination of the prevention and/or treatment of the conditions  
identified above in mammals, and by comparison of these results with the results of  
known medicaments that are used to treat these conditions, the effective dosage of the  
10 compounds of this invention can readily be determined for prevention and/or treatment of  
each desired indication. The amount of the active ingredient to be administered in the  
prevention and/or treatment of one of these conditions can vary widely according to such  
considerations as the particular compound and dosage unit employed, the mode of  
administration, the duration of treatment (including prophylactic treatment), the age and  
15 sex of the patient treated, and the nature and extent of the condition to be prevented  
and/or treated.

The total amount of the active ingredient to be administered will generally range  
from about 0.001 mg/kg to about 300 mg/kg, and preferably from about 0.10 mg/kg to  
about 150 mg/kg body weight per day. A unit dosage may contain from about 0.5 mg to  
20 about 1500 mg of active ingredient, and can be administered one or more times per day.  
The daily dosage for administration by injection, including intravenous, intramuscular,  
subcutaneous and parenteral injections, and use of infusion techniques will preferably be  
from 0.01 to 200 mg/kg of total body weight. The daily rectal dosage regimen will  
preferably be from 0.01 to 200 mg/kg of total body weight. The daily vaginal dosage  
25 regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily topical  
dosage regimen will preferably be from 0.1 to 200 mg administered between one to four  
times daily. The transdermal concentration will preferably be that required to maintain a  
daily dose of from 0.01 to 200 mg/kg. The daily inhalation dosage regimen will preferably  
be from 0.01 to 100 mg/kg of total body weight.

30 Of course the specific initial and continuing dosage regimen for each patient will  
vary according to the nature and severity of the condition as determined by the attending  
diagnostician, the activity of the specific compound employed, the age and general  
condition of the patient, time of administration, route of administration, rate of excretion of  
the drug, drug combinations, and the like. The desired mode of administration and  
35 number of doses of a compound of the present invention or a pharmaceutically  
acceptable salt or ester or composition thereof can be ascertained by those skilled in the

art using conventional prevention and/or treatment tests.

The compounds of this invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. For example, the compounds of this invention can be combined with other anti-hyper-proliferative or other indication agents, and the like, as well as with admixtures and combinations thereof.

For example, optional anti-hyper-proliferative agents which can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11<sup>th</sup> Edition of the *Merck Index*, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowledged to be used in the treatment and/or prevention of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 1225-1287, (1996), which is hereby incorporated by reference, such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-hyper-proliferative agents suitable for use with the composition of this invention include but are not limited to other anti-cancer agents such as epothilone, irinotecan, raloxifen and topotecan.

It is believed that one skilled in the art, using the preceding information and information available in the art, can utilize the present invention to its fullest extent.

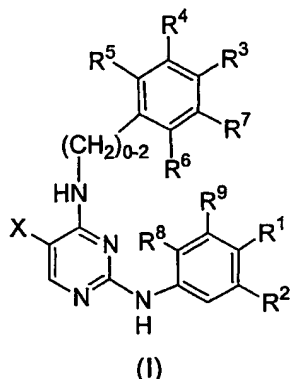
It should be apparent to one of ordinary skill in the art that changes and modifications can be made to this invention without departing from the spirit or scope of the invention as it is set forth herein. Numerous modifications and variations in the

invention as described in the above illustrative examples are expected to occur to those skilled in the art and consequently only those limitations as appear in the appended claims should be placed thereon. Accordingly it is intended in the appended claims to cover all such equivalent variations which come within the scope of the invention as claimed.

5

## WHAT IS CLAIMED IS:

## 1. A compound of Formula I



wherein

X is selected from (C<sub>1</sub>-C<sub>3</sub>)alkyl, CF<sub>3</sub>, and halo;

R<sup>1</sup> is selected from H, OH, halo, CF<sub>3</sub>, C(O)R<sup>10</sup>, NR<sup>11</sup>R<sup>11</sup>, C(NH)NH<sub>2</sub>, C(N)OH,

C(N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy,

S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, S(O)<sub>2</sub>NH<sub>2</sub>, indolyl, pyridyl, quinolyl,

(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with C(O)OH, (N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy, or with a five membered N containing heterocycle,

(C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with morpholinyl or with 1 or 2 substituents selected from OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy, 2 of said alkoxy groups optionally being joined to form dimethyldioxolanyl,

a five membered heterocycle optionally substituted with 1 or 2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl group(s), said alkyl being optionally substituted with an OH group;

a six membered heterocycle optionally substituted with C(O)OH,

C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl,

S(O)<sub>2</sub>-phenyl said phenyl being optionally substituted with 1 or 2 independently selected halo atoms, or

(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups,

phenyl substituted with one substituent selected from (C<sub>1</sub>-C<sub>6</sub>)alkoxy, CF<sub>3</sub>, CN,

N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub> group, and

(C<sub>1</sub>-C<sub>3</sub>)alkyl optionally substituted with CN, and

O-pyridyl optionally substituted with halo or (C<sub>1</sub>-C<sub>3</sub>)alkoxy;

R<sup>2</sup> is selected from H, S(O)<sub>2</sub>NH<sub>2</sub>, halo, ethynyl, OH, CF<sub>3</sub>, C(O)R<sup>10</sup>,

a five membered heterocycle, benzodioxolyl,

(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with C(O)OH, morpholinyl, with a five membered N containing heterocycle, with

NH(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups, or with  
 (C<sub>1</sub>-C<sub>3</sub>)alkoxy, said alkoxy being optionally substituted with  
 morpholinyl or imidazole,  
 (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 substituents selected from  
 N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>, OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups  
 may optionally be joined to form dimethyldioxolanyl, or with  
 1 substituent selected from imidazolyl, pyrrolidinyl, morpholinyl and  
 piperadinyl,  
 NH(C<sub>1</sub>-C<sub>6</sub>)alkyl-six membered heterocycle optionally substituted  
 with C(O)OH, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
 S(O)<sub>2</sub>-phenyl said phenyl being optionally substituted at any  
 available C atom with 1 or 2 independently selected halo  
 atoms, or with  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups,  
 phenyl substituted with 1 or 2 substituents independently selected from  
 (C<sub>1</sub>-C<sub>6</sub>)alkoxy, CN and halo, and  
 pyrazole optionally substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl;  
 R<sup>1</sup> and R<sup>2</sup> together with the C atoms to which each is attached may form a ring that is  
 fused to the phenyl ring to which they are attached to form a fused ring optionally  
 substituted with 1 or 2 substituents each independently selected from  
 (C<sub>1</sub>-C<sub>3</sub>)alkyl, (N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy, (C<sub>1</sub>-C<sub>3</sub>)alkyl-N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, C(O)NH<sub>2</sub>,  
 (N)OH, OH and SH,  
 and when the fused ring is indolyl, it may also be substituted with  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl said alkyl being optionally substituted with 1 or 2 groups each  
 selected independently from OH, N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and  
 (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups may  
 optionally be joined to form dimethyldioxolanyl;  
 R<sup>3</sup> is selected from H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, halo, S(O)<sub>2</sub>NH<sub>2</sub>, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, CF<sub>3</sub>,  
 morpholinyl, piperazinyl,  
 pyrazolyl optionally substituted with 1 or 2 independently selected  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl groups,  
 O-phenyl said phenyl being optionally substituted with halo, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, or  
 C(O)O(C<sub>1</sub>-C<sub>3</sub>)alkyl,  
 (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 substituents each independently  
 selected from OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups may  
 optionally be joined to form dimethyldioxolanyl;

R<sup>4</sup> is selected from H, halo, ethynyl, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl,

(C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 OH group(s), and

pyrazolyl optionally substituted with 1 or 2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl groups;

R<sup>3</sup> and R<sup>4</sup>, together with the C atoms to which each is attached, may form a ring that is fused to the phenyl ring to which they are attached to form a fused bi-cyclic heterocycle selected from

indolyl optionally substituted with

(C<sub>1</sub>-C<sub>6</sub>)alkyl said alkyl being optionally substituted with 1 or 2

groups each selected independently from OH,

N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and (C<sub>1</sub>-C<sub>3</sub>)alkoxy, and

wherein 2 of said alkoxy groups may optionally be joined to form dimethyldioxolanyl, and

benzotriazole optionally substituted with 1 or 2 independently selected

(C<sub>1</sub>-C<sub>6</sub>)alkyl group(s);

R<sup>5</sup> and R<sup>6</sup> are each independently selected from H, halo, and CF<sub>3</sub>;

R<sup>7</sup> is selected from H, halo and (C<sub>1</sub>-C<sub>6</sub>)alkoxy;

R<sup>8</sup> is selected from H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, and halo;

R<sup>9</sup> is selected from H, and (C<sub>1</sub>-C<sub>3</sub>)alkoxy;

R<sup>10</sup> is selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, OH, NH<sub>2</sub>, NHOR<sup>12</sup>, (C<sub>1</sub>-C<sub>6</sub>)alkoxy,

NHNHC(O)(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with CN, and

NH(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH group(s);

R<sup>11</sup> is selected from H, C(O)R<sup>10</sup>, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>3</sub>)alkyl, S(O)<sub>2</sub>N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and

S(O)<sub>2</sub>-five membered heterocycle said heterocycle being optionally

substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl and NHC(O) (C<sub>1</sub>-C<sub>3</sub>)alkyl;

R<sup>12</sup> is selected from H, (C<sub>1</sub>-C<sub>3</sub>)alkyl, and tetrahydropyranyl;

Y is selected from N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>, imidazolyl, piperidinyl, morpholinyl, pyrrolidinyl,

NH-phenyl-(C<sub>1</sub>-C<sub>6</sub>)alkoxy, NH-O-phenyl-(C<sub>1</sub>-C<sub>6</sub>)alkoxy and

NH-(C<sub>1</sub>-C<sub>6</sub>)alkoxy-phenyl;

with the provisos that

- a) when R<sup>1</sup> is H then R<sup>2</sup> must be other than H;
- b) when R<sup>2</sup> is H then R<sup>1</sup> must be other than H;
- c) when R<sup>3</sup> is H then R<sup>4</sup> must be other than H;
- d) when R<sup>4</sup> is H then R<sup>3</sup> must be other than H;
- e) when R<sup>1</sup> is C(O)OH then at least one of R<sup>2</sup>, R<sup>8</sup> and R<sup>9</sup> must be other than H;
- f) when R<sup>2</sup> is C(O)OH then at least one of R<sup>1</sup>, R<sup>8</sup> and R<sup>9</sup> must be other than H;

- g) when  $R^2$  is  $OCH_2CH_2Y$ , then  $R^1$  must be other than H;
- h) when  $R^1$  and  $R^2$  are fused then  $R^8$  and  $R^9$  are each H;
- i) when  $R^3$  and  $R^4$  together form a cyclic moiety fused to the phenyl ring to which they are attached, then  $R^5$ ,  $R^6$  and  $R^7$  must be H;
- j) when  $R^1$  is  $S(O)_2NH_2$ , and when  $(CH_2)_{0-2}$  is zero, then at least one of  $R^3$  and  $R^4$  must be selected from morpholinyl, pyrazoyl, and optionally substituted O-phenyl, or  $R^3$  and  $R^4$  together with the C atoms to which each is attached, must form a ring that is fused to the phenyl group to which they are attached to form optionally substituted indolyl or benzotriazole;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein  $R^1$  is selected from morpholinyl, optionally substituted piperazinyl, optionally substituted pyrrolidinyl, optionally substituted piperidinyl,  $NH_2$ ,  $NHC(O)(C_1-C_6)alkyl$ ,  $NHS(O)_2-imidazole-(C_1-C_3)alkyl$ ,  $N[S(O)_2(C_1-C_3)alkyl]_2$ , imidazolyl,  $C(O)NH(C_1-C_3)alkyl$ , and optionally substituted benzimidazolyl; and  $R^8$  and  $R^9$  are each H.
3. A compound of claim 1 wherein  $R^2$  is selected from halo,  $(C_1-C_3)alkyl$  and  $CF_3$ ; and  $R^8$  and  $R^9$  are each H.
4. A compound of claim 1 wherein  $R^1$  and  $R^2$  together with the C atoms to which they are attached form a ring that is fused to the phenyl ring to which  $R^1$  and  $R^2$  are attached to form a bicyclic ring that is optionally substituted indolyl; and  $R^8$  and  $R^9$  are each H.
5. A compound of claim 1 wherein  $R^3$  is selected from halo, morpholinyl,  $NH_2S(O)_2$ ,  $C(O)(C_1-C_6)alkyl$ ,  $(C_1-C_6)alkoxy$ , imidazole and  $(C_1-C_6)alkyl$ .
6. A compound of claim 5 wherein  $R^4$ ,  $R^6$  and  $R^7$  are each H.
7. A compound of claim 5 wherein  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^7$  are each H.
8. A compound of claim 1 wherein  $R^4$  is selected from halo,  $CF_3$ ,  $C(O)(C_1-C_3)alkyl$ , optionally substituted  $(C_1-C_6)alkoxy$ , and optionally substituted pyrazolyl.
9. A compound of claim 1 wherein  $R^3$ ,  $R^5$  and  $R^6$  are each H.
10. A compound of claim 8 wherein  $R^3$ ,  $R^5$  and  $R^6$  are each H.
11. A compound of claim 8 wherein  $R^5$ ,  $R^6$ , and  $R^7$  are each H.
12. A compound of claim 8 wherein  $R^3$ ,  $R^5$ ,  $R^6$ , and  $R^7$  are each H.
13. A compound of claim 5 wherein  $R^4$  is selected from halo,  $CF_3$ ,  $C(O)(C_1-C_3)alkyl$ ,  $(C_1-C_3)alkoxy$ , imidazolyl and morpholinyl.
14. A compound of claim 4 wherein  $R^4$  is selected from halo,  $CF_3$ ,  $C(O)(C_1-C_3)alkyl$ ,  $(C_1-C_3)alkoxy$ , imidazolyl and morpholinyl.
15. A compound of claim 1 wherein  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^7$  are each H.
16. A compound of claim 1 wherein X is halo.

17. A compound of claim 1 wherein R<sup>1</sup> is selected from optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkoxy, C(O)R<sup>10</sup>, optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl, indolynyl, quinolynyl and pyridinyl.
18. A compound of claim 17 wherein R<sup>8</sup> and R<sup>9</sup> are each H.
19. A compound of claim 1 wherein R<sup>2</sup> is selected from optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkoxy and optionally substituted (C<sub>1</sub>-C<sub>3</sub>)alkyl.
20. A compound of claim 19 wherein R<sup>8</sup> and R<sup>9</sup> are each H.
21. A compound of claim 1 wherein R<sup>3</sup> is halo, optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkoxy, C(O)R<sup>10</sup>, and O-phenyl, said phenyl being optionally substituted.
22. A compound of claim 21 wherein R<sup>8</sup> and R<sup>9</sup> are each H.
23. A compound of claim 1 wherein R<sup>4</sup> is selected from halo, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, ethynyl, imidazolyl and C(O)R<sup>10</sup>.
24. A compound of claim 23 wherein R<sup>6</sup> and R<sup>7</sup> are each H.
25. A compound of claim 23 wherein R<sup>4</sup>, R<sup>6</sup> and R<sup>7</sup> are each H.
26. A compound of claim 1 wherein R<sup>3</sup> and R<sup>4</sup> together with the C atoms to which they are attached form a ring that is fused to the phenyl ring to which R<sup>3</sup> and R<sup>4</sup> are attached to form a bicyclic ring that is optionally substituted indolyl; and R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are each H.
27. A compound of claim 19 wherein R<sup>3</sup> is halo, optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkoxy, C(O)R<sup>10</sup>, and O-phenyl, said phenyl being optionally substituted.
28. A compound of claim 19 wherein R<sup>8</sup> and R<sup>9</sup> are each H.
29. A compound of claim 21 wherein R<sup>1</sup> is selected from optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkoxy, C(O)R<sup>10</sup>, optionally substituted (C<sub>1</sub>-C<sub>6</sub>)alkyl, indolynyl, quinolynyl and pyridinyl.
30. A compound of claim 29 wherein R<sup>8</sup> and R<sup>9</sup> are each H.
31. A compound of claim 1 wherein R<sup>8</sup> and R<sup>9</sup> are each H.
32. A compound of claim 1 wherein X is halo, R<sup>1</sup> is selected from H, OH, C(O)R<sup>10</sup>, NR<sup>11</sup>R<sup>11</sup>, C(N)OH, C(N)(C<sub>1</sub>-C<sub>6</sub>)alkoxy, indolyl, pyridyl, quinolyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with C(O)OH, (N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy, or with a five membered N containing heterocycle, (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with morpholynyl or with 1 or 2 substituents selected from OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy, 2 of said alkoxy groups optionally being joined to form dimethyldioxolanyl, a five membered heterocycle optionally substituted with 1 or 2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl group(s), said alkyl being

optionally substituted with an OH group;  
 a six membered heterocycle optionally substituted with C(O)OH,  
 C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl,  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups,  
 phenyl substituted with one substituent selected from (C<sub>1</sub>-C<sub>6</sub>)alkoxy, CN,  
 and N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>;  
 R<sup>2</sup> is selected from H, OH, CF<sub>3</sub>, C(O)R<sup>10</sup>, a five membered heterocycle,  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with C(O)OH, morpholinyl, with a five  
 membered N containing heterocycle, with  
 NH(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups, or with  
 (C<sub>1</sub>-C<sub>3</sub>)alkoxy, said alkoxy being optionally substituted with  
 morpholinyl or imidazole,  
 (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 substituents selected from  
 N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>, OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups  
 may optionally be joined to form dimethyldioxolanyl, or with  
 1 substituent selected from imidazolyl, pyrrolidinyl, morpholinyl and  
 piperadinyl,  
 NH(C<sub>1</sub>-C<sub>6</sub>)alkyl-six membered heterocycle,  
 phenyl substituted with 1 or 2 substituents independently selected from  
 (C<sub>1</sub>-C<sub>6</sub>)alkoxy, CN and halo, and  
 pyrazole optionally substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl;  
 R<sup>1</sup> and R<sup>2</sup> together with the C atoms to which each is attached may form a ring that  
 is fused to the phenyl ring to which they are attached to form a fused ring  
 optionally substituted with 1 or 2 substituents each independently selected from  
 (C<sub>1</sub>-C<sub>3</sub>)alkyl, (N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy, (C<sub>1</sub>-C<sub>3</sub>)alkyl-N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, C(O)NH<sub>2</sub>,  
 (N)OH, and (N)O(C<sub>1</sub>-C<sub>3</sub>)alkyl,  
 and when the fused ring is indolyl, it may also be substituted with  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl said alkyl being optionally substituted with 1 or 2 groups each  
 selected independently from OH, N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and  
 (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups may  
 optionally be joined to form dimethyldioxolanyl;  
 R<sup>3</sup> is selected from H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, halo, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, morpholinyl, piperazinyl,  
 pyrazolyl optionally substituted with 1 or 2 independently selected  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl groups,  
 O-phenyl said phenyl being optionally substituted with halo, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, or  
 C(O)O(C<sub>1</sub>-C<sub>3</sub>)alkyl,

(C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 substituents each independently selected from OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups may optionally be joined to form dimethyldioxolanyl;

R<sup>4</sup> is selected from H, halo, ethynyl, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 OH group(s), and pyrazolyl optionally substituted with 1 or 2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl groups;

R<sup>3</sup> and R<sup>4</sup>, together with the C atoms to which each is attached, may form a ring that is fused to the phenyl ring to which they are attached to form a fused bi-cyclic heterocycle selected from

indolyl optionally substituted with

(C<sub>1</sub>-C<sub>6</sub>)alkyl said alkyl being optionally substituted with 1 or 2 groups each selected independently from OH,

N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and (C<sub>1</sub>-C<sub>3</sub>)alkoxy, and

wherein 2 of said alkoxy groups may optionally be joined to form dimethyldioxolanyl, and

benzotriazole;

R<sup>5</sup> and R<sup>6</sup> are each H;

R<sup>7</sup> is selected from H, halo and (C<sub>1</sub>-C<sub>6</sub>)alkoxy;

R<sup>8</sup> is H;

R<sup>9</sup> is selected from H and (C<sub>1</sub>-C<sub>3</sub>)alkoxy;

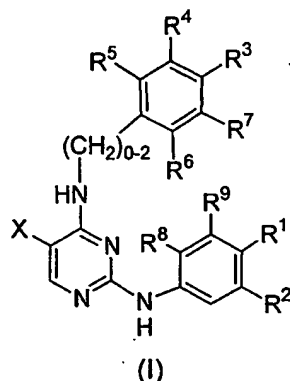
R<sup>10</sup> is selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, NHOR<sup>12</sup>, (C<sub>1</sub>-C<sub>6</sub>)alkoxy and NH(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH group(s);

R<sup>11</sup> is selected from H, C(O)R<sup>10</sup>, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>3</sub>)alkyl, S(O)<sub>2</sub>N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and S(O)<sub>2</sub>-five membered heterocycle said heterocycle being optionally substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl and NHC(O) (C<sub>1</sub>-C<sub>3</sub>)alkyl;

R<sup>12</sup> is selected from H, (C<sub>1</sub>-C<sub>3</sub>)alkyl, and tetrahydropyranyl; and

Y is selected from N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>, imidazolyl, piperidinyl, and morpholinyl.

33. A composition comprising a compound of Formula I



wherein

X is selected from (C<sub>1</sub>-C<sub>3</sub>)alkyl, CF<sub>3</sub>, and halo;

R<sup>1</sup> is selected from H, OH, halo, CF<sub>3</sub>, C(O)R<sup>10</sup>, NR<sup>11</sup>R<sup>11</sup>, C(NH)NH<sub>2</sub>, C(N)OH,

C(N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy,

S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, S(O)<sub>2</sub>NH<sub>2</sub>, indolyl, pyridyl, quinolyl,

(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with C(O)OH, (N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy, or with a five membered N containing heterocycle,

(C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with morpholynyl or with 1 or 2 substituents selected from OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy, 2 of said alkoxy groups optionally being joined to form dimethyldioxolanyl,

a five membered heterocycle optionally substituted with 1 or

2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl group(s), said alkyl being optionally substituted with an OH group;

a six membered heterocycle optionally substituted with C(O)OH,

C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl,

S(O)<sub>2</sub>-phenyl said phenyl being optionally substituted with 1 or 2 independently selected halo atoms, or

(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups,

phenyl substituted with one substituent selected from (C<sub>1</sub>-C<sub>6</sub>)alkoxy, CF<sub>3</sub>, CN,

N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub> group, and

(C<sub>1</sub>-C<sub>3</sub>)alkyl optionally substituted with CN, and

O-pyridyl optionally substituted with halo or (C<sub>1</sub>-C<sub>3</sub>)alkoxy;

R<sup>2</sup> is selected from H, S(O)<sub>2</sub>NH<sub>2</sub>, halo, ethynyl, OH, CF<sub>3</sub>, C(O)R<sup>10</sup>,

a five membered heterocycle, benzodioxolyl,

(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with C(O)OH, morpholynyl, with a five membered N containing heterocycle, with

NH(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups, or with

(C<sub>1</sub>-C<sub>3</sub>)alkoxy, said alkoxy being optionally substituted with

morpholinyl or imidazole,  
 (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 substituents selected from  
 N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>, OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups  
 may optionally be joined to form dimethyldioxolanyl, or with  
 1 substituent selected from imidazolyl, pyrrolidinyl, morpholinyl and  
 piperadinyl,  
 NH(C<sub>1</sub>-C<sub>6</sub>)alkyl-six membered heterocycle optionally substituted  
 with C(O)OH, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
 S(O)<sub>2</sub>-phenyl said phenyl being optionally substituted at any  
 available C atom with 1 or 2 independently selected halo  
 atoms, or with  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups,  
 phenyl substituted with 1 or 2 substituents independently selected from  
 (C<sub>1</sub>-C<sub>6</sub>)alkoxy, CN and halo, and  
 pyrazole optionally substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl;  
 R<sup>1</sup> and R<sup>2</sup> together with the C atoms to which each is attached may form a ring that is  
 fused to the phenyl ring to which they are attached to form a fused ring optionally  
 substituted with 1 or 2 substituents each independently selected from  
 (C<sub>1</sub>-C<sub>3</sub>)alkyl, (N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy, (C<sub>1</sub>-C<sub>3</sub>)alkyl-N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, C(O)NH<sub>2</sub>,  
 (N)OH, OH and SH,  
 and when the fused ring is indolyl, it may also be substituted with  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl said alkyl being optionally substituted with 1 or 2 groups each  
 selected independently from OH, N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and  
 (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups may  
 optionally be joined to form dimethyldioxolanyl;  
 R<sup>3</sup> is selected from H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, halo, S(O)<sub>2</sub>NH<sub>2</sub>, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, CF<sub>3</sub>,  
 morpholinyl, piperazinyl,  
 pyrazolyl optionally substituted with 1 or 2 independently selected  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl groups,  
 O-phenyl said phenyl being optionally substituted with halo, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, or  
 C(O)O(C<sub>1</sub>-C<sub>3</sub>)alkyl,  
 (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 substituents each independently  
 selected from OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups may  
 optionally be joined to form dimethyldioxolanyl;  
 R<sup>4</sup> is selected from H, halo, ethynyl, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl,  
 (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 OH group(s), and

pyrazolyl optionally substituted with 1 or 2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl groups;

R<sup>3</sup> and R<sup>4</sup>, together with the C atoms to which each is attached, may form a ring that is fused to the phenyl ring to which they are attached to form a fused bi-cyclic heterocycle selected from

indolyl optionally substituted with

(C<sub>1</sub>-C<sub>6</sub>)alkyl said alkyl being optionally substituted with 1 or 2

groups each selected independently from OH,

N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and (C<sub>1</sub>-C<sub>3</sub>)alkoxy, and

wherein 2 of said alkoxy groups may optionally be joined to form dimethyldioxolanyl, and

benzotriazole optionally substituted with 1 or 2 independently selected

(C<sub>1</sub>-C<sub>6</sub>)alkyl group(s);

R<sup>5</sup> and R<sup>6</sup> are each independently selected from H, halo, and CF<sub>3</sub>;

R<sup>7</sup> is selected from H, halo and (C<sub>1</sub>-C<sub>6</sub>)alkoxy;

R<sup>8</sup> is selected from H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, and halo;

R<sup>9</sup> is selected from H, and (C<sub>1</sub>-C<sub>3</sub>)alkoxy;

R<sup>10</sup> is selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, OH, NH<sub>2</sub>, NHOR<sup>12</sup>, (C<sub>1</sub>-C<sub>6</sub>)alkoxy,

NHNHC(O)(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with CN, and

NH(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH group(s);

R<sup>11</sup> is selected from H, C(O)R<sup>10</sup>, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>3</sub>)alkyl, S(O)<sub>2</sub>N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and

S(O)<sub>2</sub>-five membered heterocycle said heterocycle being optionally

substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl and NHC(O) (C<sub>1</sub>-C<sub>3</sub>)alkyl;

R<sup>12</sup> is selected from H, (C<sub>1</sub>-C<sub>3</sub>)alkyl, and tetrahydropyranyl;

Y is selected from N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>, imidazolyl, piperidinyl, morpholinyl, pyrrolidinyl,

NH-phenyl-(C<sub>1</sub>-C<sub>6</sub>)alkoxy, NH-O-phenyl-(C<sub>1</sub>-C<sub>6</sub>)alkoxy and

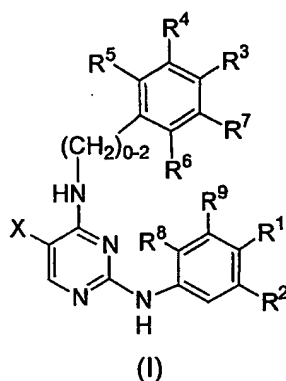
NH-(C<sub>1</sub>-C<sub>6</sub>)alkoxy-phenyl;

with the provisos that

- a) when R<sup>1</sup> is H then R<sup>2</sup> must be other than H;
- b) when R<sup>2</sup> is H then R<sup>1</sup> must be other than H;
- c) when R<sup>3</sup> is H then R<sup>4</sup> must be other than H;
- d) when R<sup>4</sup> is H then R<sup>3</sup> must be other than H;
- e) when R<sup>1</sup> is C(O)OH then at least one of R<sup>2</sup>, R<sup>8</sup> and R<sup>9</sup> must be other than H;
- f) when R<sup>2</sup> is C(O)OH then at least one of R<sup>1</sup>, R<sup>8</sup> and R<sup>9</sup> must be other than H;
- g) when R<sup>2</sup> is OCH<sub>2</sub>CH<sub>2</sub>Y, then R<sup>1</sup> must be other than H;
- h) when R<sup>1</sup> and R<sup>2</sup> are fused then R<sup>8</sup> and R<sup>9</sup> are each H;

- i) when R<sup>3</sup> and R<sup>4</sup> together form a cyclic moiety fused to
  - j) the phenyl ring to which they are attached, then R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> must be H;
  - k) when R<sup>1</sup> is S(O)<sub>2</sub>NH<sub>2</sub>, and when (CH<sub>2</sub>)<sub>0-2</sub> is zero, then at least one of R<sup>3</sup> and R<sup>4</sup> must be selected from morpholinyl, pyrazoyl, and optionally substituted O-phenyl, or R<sup>3</sup> and R<sup>4</sup> together with the C atoms to which each is attached, must form a ring that is fused to the phenyl group to which they are attached to form optionally substituted indolyl or benzotriazole;
- or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

34. A method of treating a hyper-proliferative disorder comprising administering to a patient in need thereof an effective amount of a compound of Formula I



wherein

X is selected from (C<sub>1</sub>-C<sub>3</sub>)alkyl, CF<sub>3</sub>, and halo;

R<sup>1</sup> is selected from H, OH, halo, CF<sub>3</sub>, C(O)R<sup>10</sup>, NR<sup>11</sup>R<sup>11</sup>, C(NH)NH<sub>2</sub>, C(N)OH,

C(N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy,

S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, S(O)<sub>2</sub>NH<sub>2</sub>, indolyl, pyridyl, quinolyl,

(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with C(O)OH, (N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy, or with a five membered N containing heterocycle,

(C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with morpholinyl or with 1 or 2 substituents selected from OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy, 2 of said alkoxy groups optionally being joined to form dimethyldioxolanyl,

a five membered heterocycle optionally substituted with 1 or 2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl group(s), said alkyl being optionally substituted with an OH group;

a six membered heterocycle optionally substituted with C(O)OH,

C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl,

S(O)<sub>2</sub>-phenyl said phenyl being optionally substituted with 1 or 2

independently selected halo atoms, or  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups,  
 phenyl substituted with one substituent selected from (C<sub>1</sub>-C<sub>6</sub>)alkoxy, CF<sub>3</sub>, CN,  
 N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub> group, and  
 (C<sub>1</sub>-C<sub>3</sub>)alkyl optionally substituted with CN, and  
 O-pyridyl optionally substituted with halo or (C<sub>1</sub>-C<sub>3</sub>)alkoxy;  
 R<sup>2</sup> is selected from H, S(O)<sub>2</sub>NH<sub>2</sub>, halo, ethynyl, OH, CF<sub>3</sub>, C(O)R<sup>10</sup>,  
 a five membered heterocycle, benzodioxolyl,  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with C(O)OH, morpholinyl, with a five  
 membered N containing heterocycle, with  
 NH(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups, or with  
 (C<sub>1</sub>-C<sub>3</sub>)alkoxy, said alkoxy being optionally substituted with  
 morpholinyl or imidazole,  
 (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 substituents selected from  
 N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>, OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups  
 may optionally be joined to form dimethyldioxolanyl, or with  
 1 substituent selected from imidazolyl, pyrrolidinyl, morpholinyl and  
 piperadinyl,  
 NH(C<sub>1</sub>-C<sub>6</sub>)alkyl-six membered heterocycle optionally substituted  
 with C(O)OH, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
 S(O)<sub>2</sub>-phenyl said phenyl being optionally substituted at any  
 available C atom with 1 or 2 independently selected halo  
 atoms, or with  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH groups,  
 phenyl substituted with 1 or 2 substituents independently selected from  
 (C<sub>1</sub>-C<sub>6</sub>)alkoxy, CN and halo, and  
 pyrazole optionally substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl;  
 R<sup>1</sup> and R<sup>2</sup> together with the C atoms to which each is attached may form a ring that is  
 fused to the phenyl ring to which they are attached to form a fused ring optionally  
 substituted with 1 or 2 substituents each independently selected from  
 (C<sub>1</sub>-C<sub>3</sub>)alkyl, (N)(C<sub>1</sub>-C<sub>3</sub>)alkoxy, (C<sub>1</sub>-C<sub>3</sub>)alkyl-N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, C(O)NH<sub>2</sub>,  
 (N)OH, OH and SH,  
 and when the fused ring is indolyl, it may also be substituted with  
 (C<sub>1</sub>-C<sub>6</sub>)alkyl said alkyl being optionally substituted with 1 or 2 groups each  
 selected independently from OH, N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and  
 (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups may

optionally be joined to form dimethyldioxolanyl;

R<sup>3</sup> is selected from H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, halo, S(O)<sub>2</sub>NH<sub>2</sub>, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, CF<sub>3</sub>, morpholinyl, piperazinyl, pyrazolyl optionally substituted with 1 or 2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl groups, O-phenyl said phenyl being optionally substituted with halo, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, or C(O)O(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 substituents each independently selected from OH and (C<sub>1</sub>-C<sub>3</sub>)alkoxy wherein 2 of said alkoxy groups may optionally be joined to form dimethyldioxolanyl;

R<sup>4</sup> is selected from H, halo, ethynyl, C(O)(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with 1 or 2 OH group(s), and pyrazolyl optionally substituted with 1 or 2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl groups;

R<sup>3</sup> and R<sup>4</sup>, together with the C atoms to which each is attached, may form a ring that is fused to the phenyl ring to which they are attached to form a fused bi-cyclic heterocycle selected from indolyl optionally substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl said alkyl being optionally substituted with 1 or 2 groups each selected independently from OH, N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and (C<sub>1</sub>-C<sub>3</sub>)alkoxy, and wherein 2 of said alkoxy groups may optionally be joined to form dimethyldioxolanyl, and benzotriazole optionally substituted with 1 or 2 independently selected (C<sub>1</sub>-C<sub>6</sub>)alkyl group(s);

R<sup>5</sup> and R<sup>6</sup> are each independently selected from H, halo, and CF<sub>3</sub>;

R<sup>7</sup> is selected from H, halo and (C<sub>1</sub>-C<sub>6</sub>)alkoxy;

R<sup>8</sup> is selected from H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, and halo;

R<sup>9</sup> is selected from H, and (C<sub>1</sub>-C<sub>3</sub>)alkoxy;

R<sup>10</sup> is selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, OH, NH<sub>2</sub>, NHOR<sup>12</sup>, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, NHNHC(O)(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with CN, and NH(C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with 1 or 2 OH group(s);

R<sup>11</sup> is selected from H, C(O)R<sup>10</sup>, S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>3</sub>)alkyl, S(O)<sub>2</sub>N[(C<sub>1</sub>-C<sub>3</sub>)alkyl]<sub>2</sub>, and S(O)<sub>2</sub>-five membered heterocycle said heterocycle being optionally substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl and NHC(O) (C<sub>1</sub>-C<sub>3</sub>)alkyl;

R<sup>12</sup> is selected from H, (C<sub>1</sub>-C<sub>3</sub>)alkyl, and tetrahydropyranyl;

Y is selected from N[(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>, imidazolyl, piperidinyl, morpholinyl, pyrrolidinyl, NH-phenyl-(C<sub>1</sub>-C<sub>6</sub>)alkoxy, NH-O-phenyl-(C<sub>1</sub>-C<sub>6</sub>)alkoxy and NH-(C<sub>1</sub>-C<sub>6</sub>)alkoxy-phenyl;

with the provisos that

- a) when R<sup>1</sup> is H then R<sup>2</sup> must be other than H;
- b) when R<sup>2</sup> is H then R<sup>1</sup> must be other than H;
- c) when R<sup>3</sup> is H then R<sup>4</sup> must be other than H;
- d) when R<sup>4</sup> is H then R<sup>3</sup> must be other than H;
- e) when R<sup>1</sup> is C(O)OH then at least one of R<sup>2</sup>, R<sup>8</sup> and R<sup>9</sup> must be other than H;
- f) when R<sup>2</sup> is C(O)OH then at least one of R<sup>1</sup>, R<sup>8</sup> and R<sup>9</sup> must be other than H;
- g) when R<sup>2</sup> is OCH<sub>2</sub>CH<sub>2</sub>Y, then R<sup>1</sup> must be other than H;
- h) when R<sup>1</sup> and R<sup>2</sup> are fused then R<sup>8</sup> and R<sup>9</sup> are each H;
- i) when R<sup>3</sup> and R<sup>4</sup> together form a cyclic moiety fused to
- j) the phenyl ring to which they are attached, then R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> must be H;
- k) when R<sup>1</sup> is S(O)<sub>2</sub>NH<sub>2</sub>, and when (CH<sub>2</sub>)<sub>0-2</sub> is zero, then at least one of R<sup>3</sup> and R<sup>4</sup> must be selected from morpholinyl, pyrazoyl, and optionally substituted O-phenyl, or R<sup>3</sup> and R<sup>4</sup> together with the C atoms to which each is attached, must form a ring that is fused to the phenyl group to which they are attached to form optionally substituted indolyl or benzotriazole;

or a pharmaceutically acceptable salt thereof.

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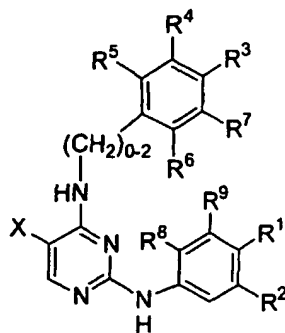
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(54) Title: 2-4-(DI-PHENYL-AMINO)-PYRIMIDINE DERIVATIVES USEFUL FOR TREATING HYPER-PROLIFERATIVE DISORDERS



(I)

(57) Abstract: The present invention relates to a 2-4-(diphenyl-amino)-pyrimidinyl compound of Formula I useful for treating hyper-proliferative disorders.



— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/032997 A (STEEGMAIER MARTIN ; KRIST BERND (AT); SPEVAK WALTER (AT); SCHOOP ANDRE) 24 April 2003 (2003-04-24) page 197, example 9; page 198, example 17; claim 1	1-34
P,X	WO 03/031406 A (IRM LLC ; DING QIANG (US); DING SHENG (US); GRAY NATHANAE S (US)) 17 April 2003 (2003-04-17) claim 1; example 177; table 4	1-34
X	WO 01/64655 A (BREAULT GLORIA ANNE ; PEASE ELIZABETH JANET (GB); ASTRAZENECA UK LTD ( ) 7 September 2001 (2001-09-07) claim 1; examples 21-40	1-34
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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International Application No  
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